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15

LEADING ARTICLES

Seventy-five years on
H. A. F. Dudley 1

dominal tuberculosis
K. Kapoor and L. K. Sharma 2

riple therapy in cadaver renal transplantation
M. Jones, J. A. Murie, R. D. Allen, A. Ting and P. J. Morris 4

currence of varices after oesophageal transection; intra-operative and postoperative assessment by doscopy
N. Koyanagi, Y. Iso, H. Higashi, S. Kitano and K. Sugimachi 9

Results of resection of gastric cancer extending to adjacent organs
D. Korenaga, T. Okamura, H. Baba, A. Saito and K. Sugimachi 12

Surgical management of bleeding gastric ulceration
P. N. Rogers, W. R. Murray, R. Shaw and S. Brar 16

Splenectomy and renal allograft survival in the rat
D. Cranston, Kathryn J. Wood and P. J. Morris 18

Growth rate of human tumour xenografts measured in nude mice by *in vivo* cast modelling
A. G. T. W. Fiennes 23

Improvements in the treatment and prognosis of colorectal carcinoma
H. J. Järvinen, J. Ovaska and J.-P. Mecklin 25

Prognostic significance of DNA ploidy in colorectal cancer: a prospective flow cytometric study
D. J. Jones, M. Moore and P. F. Schofield 28

Penile incarceration by a metallic object (surgical workshop)
B. B. Sinha 33

Complete rectal prolapse: the anatomical and functional results of treatment by an extended abdominal rectopexy
C. V. Mann and C. Hoffman 34

Tubercular fistula *in ano*
H. S. Shukla, S. C. Gupta, G. Singh and P. A. Singh 38

Assessment of microtransducers in anorectal manometry
R. Miller, D. C. C. Bartolo, A. M. Roe and N. J. McC. Mortensen 40

Anorectal sampling: a comparison of normal and incontinent patients
R. Miller, D. C. C. Bartolo, F. Cervero and N. J. McC. Mortensen 44

Testicular torsion after previous orchidopexy (case report)
D. A. Steinbrüchel and M. K. Hansen 47

Prospective study of the effects of postanal repair in neurogenic faecal incontinence
N. R. Womack, J. F. B. Morrison and N. S. Williams 48

Investigation of anorectal function
Richelle J. F. Felt-Bersma, Elly C. Klinkenberg-Knol and S. G. M. Meuwissen 53

Anal fissure in Crohn's disease
J. L. Sweeney, Jean K. Ritchie and R. J. Nicholls 56

pendicitis and schistosomiasis
l-Kraida, A. Giangreco, M. U. Shaikh and A. Al-Shehri 58

sis after simple incision and drainage for a first-episode acute pilonidal abscess
ensen and H. Harling 60

atment of 'inoperable' neck nodes using surgical clearance and postoperative interstitial irradiation
. Stafford and D. Dearnaley 62

rescribing information

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Use of myocutaneous flaps for primary cover following lymph node dissection for malignant melanoma 65
R. H. Morgan, K. Horgan and L. E. Hughes

Acral (volar–subungual) melanoma in Auckland, New Zealand 69
J. H. F. Shaw and J. B. Koea

Omental viability and incisional herniation after omental transposition for the repair of chest wall defects (case report) 72
M. R. Pittam, P. M. Lamont and J. Meirion Thomas

Effect of epidural anaesthesia on intestinal blood flow 73
K. Johansson, H. Ahn, J. Lindhagen and U. Tryselius

Maximal isokinetic muscle strength in patients with primary hyperparathyroidism before and after parathyroid surgery 77
Charlotte Joborn, H. Joborn, J. Rastad, G. Åkerström and S. Ljunghall

Platelet aggregation on peritoneal tube grafts and double velour grafts in the inferior vena cava of the pig 81
Else B. Ribbe, B.-A. Jönsson, L. E. H. Norgren, S.-E. Strand and J. L. Thörne

Small bowel volvulus complicating intestinal ascariasis in children 86
R. Wiersma and G. P. Hadley

Pancreatic abscess: results of prolonged irrigation of the pancreatic bed after surgery 88
M. L. Nicholson, N. J. McC. Mortensen and H. J. Espiner

CORRESPONDENCE 92

BOOK REVIEWS 94

NOTICE AND ANNOUNCEMENTS 96

Cover picture

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Br. J. Surg. 1988, Vol. 75, January, 1

Seventy-five years on

There are many who might say that anniversaries are contrived events, arranged merely to highlight the activities of the institution – such as our Journal – that they celebrate or to raise the profile of those currently in office. My Editorial Committee is sufficiently robust to allow that both are true and not to be agonized over. Milestones would not be there unless they were an indication of what we believe is progress towards a goal which still may be over the horizon. Our Journal is the outcome of the fertile and expansive mind of Moynihan and let us hope that he would in no way disapprove of how it presents itself today. It has, we believe, moved beyond his original vision of a mouthpiece for British surgery to become an international publication. We find this pleasing but also recognize that we live in a rapidly changing world which Moynihan and his colleagues would have problems in recognizing.

At the moment we are accustomed to receiving a journal as a recognizable body of hard copy presented with reasonable style and readable wherever we are – in an aeroplane, beside the fire or at a library table. The optical disk, the facsimile reproduction, the photocopy licensed reproduction all loom ever nearer as competitors to our conventional, satisfactory, yet cumbersome publication. As yet we know not how they will develop but, to use a somewhat trite phrase, we are 'keeping a close eye on the matter'. We feel it likely that within 5 years most manuscripts will reach the BJS office on disk or down a wire and, even if they are presented as old-fashioned paper, will immediately be transferred by a document reader into the memory of a computer, so simplifying the editing and printing process.

Nineteen eighty-eight, our anniversary year, will herald another development of the Journal which aims to enhance our global view. To the east, India will have its own edition of the Journal; this will not be a new publication but the monthly issue of the Journal bound and distributed in that country to overcome some of the problems in economics and communication that have limited our circulation and influence there. To the south and west, a Spanish language edition will be marketed first in the Iberian peninsula and, soon we hope, thereafter throughout the South American continent. For the latter we have to thank Professor C. Pera of Barcelona and Mr Adrian Marston of the Middlesex Hospital, both members of our editorial board, who have worked hard to bring this highly desirable innovation to fruition.

To meet these new challenges we are continually looking at our organization and how we might improve our access to specialized advice. For those who are interested page *iv* shows the current 'organogram' of the Journal and the reader will see that we have decided it is past the time that we had the benefit of formal statistical advice. Surgeons are amongst the most avid users (and some would say abusers) of statistical techniques and we are conscious of the need for detached and objective criticism of our sometimes amateur approach. We are confident that we will become the 'standard-setter' in this field.

H. A. F. Dudley

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Abdominal tuberculosis

Abdominal tuberculosis, a disease with worldwide distribution, is uncommon in the West but is still prevalent in developing countries like India. However, its frequency has recently increased in countries such as the UK largely due to the arrival of Asian immigrants[1]. The fallacy that tuberculosis is a rare disease may lead to missed diagnosis and delay in institution of treatment.

Abdominal tuberculosis may involve the gastrointestinal tract, peritoneum and mesenteric lymph nodes. The commonest sites of involvement are the terminal ileum and ileocaecal region, followed by the jejunum and colon. Multiple sites of involvement are common. The intestinal lesions are either ulceroconstrictive (small intestine) or hypertrophic (ileocaecal). Tuberculosis is the commonest cause of a stenotic intestinal lesion in tropical countries like India[2] whereas Crohn's disease and malignancy predominate in the West. Ileocaecal lesions also have to be differentiated from an appendicular mass and amoeboma. Increased amounts of mesenteric fat, enlarged lymph nodes with caseation, peritoneal tubercles and ascites are characteristic. Histopathological examination reveals epithelioid cell granulomas with Langhan's giant cells and central caseation necrosis. Acid fast bacilli are difficult to demonstrate on culture from intestinal lesions[2].

The disease is common in young adults and females are more often affected than males. It may have a chronic, acute-on-chronic or acute presentation. With its vague symptoms and non-specific signs it may mimic any disease and challenge diagnostic skills—even in areas where the disease is prevalent a correct clinical diagnosis is made in only one-half of the cases[3]. Ulcerative lesions of the small intestine present with chronic abdominal pain and diarrhoea, and malabsorption is common. Small intestinal strictures and hypertrophic ileocaecal lesions cause subacute intestinal obstruction. Peritoneal tuberculosis presents with ascites or subacute intestinal obstruction due to adhesions. Nodal tuberculosis is usually associated with intestinal or peritoneal lesions. A lump is often palpable in patients with abdominal tuberculosis; it is formed by the hypertrophic ileocaecal lesion, mass of matted lymph nodes, rolled-up omentum or loculated ascites. Fever, night sweats, malaise, anorexia and weight-loss may be present. Associated pulmonary tuberculosis is uncommon and peripheral lymph nodes are rarely involved. Acute-on-chronic intestinal obstruction is the commonest complication of abdominal tuberculosis. Perforation proximal to a stricture is not uncommon.

Haematological and immunological (Heaf, Montoux) tests normally show non-specific changes. Evidence of tuberculosis (active or healed) on chest X-ray supports the diagnosis. Abdominal plain films may show dilated loops, fluid levels, ascites, calcified lymph nodes and enteroliths. However, normal chest and abdominal radiographs do not rule out abdominal tuberculosis and barium studies are indicated; barium enema visualizes ileocaecal lesions whereas lesions of the small intestine are better seen on barium meal and follow-through or small bowel enema. Radiographic appearances are, however, non-specific and may give both false-negative and false-positive results. It may be difficult to differentiate tuberculosis from Crohn's disease and carcinoma, and barium studies are positive in only two-thirds of cases[4]. In patients with ascites, peritoneal tap reveals a clear straw-coloured exudate with a protein concentration of more than 25 g/l and a lymphocyte count exceeding 1000 cells/mm^3; acid fast bacilli can be cultured[5]. Percutaneous[5], laparoscopic[6] and open peritoneal biopsy under local anaesthesia[7] are helpful. Colonoscopic biopsy has been used in the diagnosis of ileocaecal and colonic lesions[8]. In cases where the diagnosis remains equivocal, diagnostic laparotomy may be required.

Patients with acute intestinal obstruction, perforation and acute peritonitis may require emergency surgery. However, conservative treatment is advocated initially for tubercular intestinal obstruction whenever possible as the mortality of emergency surgery is high. The majority of the patients improve and can be operated upon 2–4 weeks later[9]. Tubercular perforations are often associated with strictures which can be resected along with closure of the perforation[10]. In acute tuberculous peritonitis the abdomen is closed without drainage after removing the ascitic fluid and obtaining a peritoneal biopsy[11].

Surgery is recommended for intestinal lesions because medical treatment results in healing by fibrosis thus increasing or causing obstruction and perforation. All patients

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should receive a full course of anti-tubercular treatment such as ethambutol (6–8 weeks) plus rifampicin and isoniazid for 18 months after operation[12]. By-pass procedures (entero-enterostomy and ileotransverse colostomy) result in blind loops, may cause obstruction and malabsorption and are not recommended. Small intestinal strictures may be treated by stricture-plasty but resection is performed if the lumen is completely obstructed or if there are multiple strictures in a short segment[13]. A limited ileocaecal resection with a 5 cm margin is preferred to right hemicolectomy for ileocaecal lesions[14]. Peritoneal and nodal tuberculosis are treated with anti-tuberculous drugs; there is some evidence that addition of steroids may prevent adhesion formation.

Despite recent advances in surgery and the availability of specific antituberculous drugs, the mortality of abdominal tuberculosis remains high. It can be reduced only by timely diagnosis and judicious treatment as outlined above.

V. K. Kapoor
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4–8

Triple therapy in cadaver renal transplantation

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One hundred consecutive first (n = 72) *and regrafted* (n = 28) *cadaver renal allograft recipients were immunosuppressed with cyclosporin, azathioprine and prednisolone (triple therapy) and followed for a median of 17·3 months (range, 7–26 months). Actuarial patient survival at 12 and 24 months was 97·7 per cent. Actuarial graft survival at 12 and 24 months was 79·5 per cent (first graft recipients 81·3 per cent and regrafted recipients 75 per cent). HLA-DR matching significantly improved graft survival which was 93 per cent at 1 year in patients given HLA-DR compatible kidneys, compared with 83 and 54 per cent, respectively, in patients who received kidneys mismatched for one or two HLA-DR antigens. There were 0·8 (s.d. = 0·7) episodes of acute rejection per patient during the first 3 months after transplantation. Triple therapy provides effective immunosuppression without evidence of over immunosuppression and reduces the incidence of cyclosporin side-effects. Although acute nephrotoxicity was uncommon, serum creatinine remained elevated 6 and 12 months after transplantation.*

Keywords: Triple therapy, cyclosporin, renal transplantation

Cyclosporin A has improved allograft survival in cadaver renal transplantation and this has been associated with a reduction in episodes of acute rejection and major infection[1,2]. However, cyclosporin A causes a dose-related impairment of renal function which is largely reversible in the short-term[3] but may result in parenchymal damage with permanent renal dysfunction[4–6]. Furthermore, kidneys damaged from ischaemia at the time of transplantation may be more susceptible to cyclosporin nephrotoxicity[7–9]. Lower doses of cyclosporin A reduce the impairment of renal function and may limit histological damage. However the optimal immunosuppressive dose of cyclosporin A for each patient cannot be predicted and low-dose cyclosporin A with low blood levels or rapid dose reduction may precipitate acute rejection[10]. The combination of low-dose cyclosporin A, azathioprine and prednisolone (triple therapy) has been used in several centres[2,11–13] in an attempt to maintain the immunosuppressive advantages of cyclosporin A while reducing nephrotoxicity and improving renal function. In this report we present our experience with triple therapy in 100 consecutive patients who received a cadaver renal transplant.

Patients and methods

A total of 97 adult patients received 100 consecutive cadaver kidneys from May 1985 to November 1986 This analysis was performed in July 1987. Mean follow-up was 16 9 (s.d. = 5·6) months (range, 7–26 months; median, 17·3 months). Operations were performed on 63 male patients and 37 female patients whose ages ranged from 17 to 64 years with a mean of 41 6 (s.d. = 13) years Twenty-two patients were greater than 55 years of age and twenty-eight patients received a second, third or fourth graft. Twenty patients were highly sensitized (panel reactivity >90 per cent). Recipients were selected on the basis of matching for HLA-DR as far as possible. Twenty-nine patients had no DR mismatches and 47 patients a single DR mismatch. Two donors could not be satisfactorily DR typed. Transplantation was performed in the presence of a positive crossmatch in 24 patients when the positive crossmatch was considered to be due to autoreactive antibodies against donor T and/or B lymphocytes or when the positive crossmatch was due to HLA antibodies in old but not current sera[14]. Ninety-five patients had been deliberately transfused with whole blood in the months before transplantation.

In 45 cases patients received oral cyclosporin 10 mg kg^{-1} day^{-1} pre-operatively and daily. In the other 55 cases patients received intravenous cyclosporin 4 mg kg^{-1} day^{-1} immediately postoperatively and daily for the first 4 days, and 10 mg kg^{-1} day^{-1} orally from day 3. The dose was adjusted to maintain trough whole blood levels in the range 400–800 ng ml^{-1} or plasma levels in the range 50–150 ng ml^{-1}. Trough cyclosporin levels were measured by radioimmunoassay (Sandoz, Basle, Switzerland). In the first 47 transplants this was carried out on a heparinized plasma sample stored at room temperature for 2 h before separation In the last 53 transplants, whole blood levels were estimated after freezing using ethylenediaminetetraacetic acid as the anticoagulant. In seven patients, the initial cyclosporin dose was reduced because of early non-function or a prolonged cold ischaemic time. All other patients received cyclosporin according to the protocol. All patients received azathioprine 1·5 mg kg^{-1} day^{-1} and prednisolone 200 mg day^{-1} pre-operatively and daily. Prednisolone was reduced by 1 mg every 2 weeks from day 90 to a maintenance dose of 10 mg day^{-1}. Highly sensitized patients (panel reactivity >90 per cent) received methylprednisolone 500 mg day^{-1} intra-operatively and daily for the next 2 days.

Rejection was diagnosed clinically and confirmed histologically by percutaneous biopsy. Only 4 of the 100 transplants were not biopsied, for technical reasons Rejection was treated with methylprednisolone 500 mg daily for 3–6 days. Twelve patients with steroid resistant rejection, proven on biopsy, were treated with rabbit antithymocyte globulin, ATG (Fresenius, Munich, FRG) Acute cyclosporin toxicity was defined as a rise in serum creatinine of 20 per cent, which was treated successfully by a dose reduction of cyclosporin Delayed graft function was defined as a failure to pass >1500 mls of urine in the first 24 h with an associated drop in serum creatinine or requirement for dialysis in the first 7 days Graft loss was defined as loss from death with a functioning graft as well as loss from graft nephrectomy, return to permanent dialysis, or re-transplantation. The time of graft loss was recorded as the time of death or return to dialysis

In all, 85 kidneys were harvested after *in situ* perfusion and stored in ice and 15 kidneys were received from the UK Transplant Service, with a mean warm ischaemic time for the group of 5 min. The mean total cold ischaemic time for all kidneys was 22·2 (s.d. = 5·4) h. A standard surgical procedure was used for implantation of the kidney. The central venous pressure was monitored in all patients and volume loading, mannitol 12·5 g and frusemide 80 mg were administered intra-operatively Whole blood was given within 48 h of operation to 50 patients. Patients underwent routine percutaneous biopsy at days 7, 21, 90 and 365 and at other times when clinically indicated.

Patients were followed routinely in the transplant clinic and represent a consecutive series with no exclusions from the study or subsequent analysis. Survival was calculated by the life-table method and corresponding significance levels by the log rank test. The Mann–Whitney *U* test and the Student's *t* test have been used to compare populations. Values are expressed as the mean ± s.d.

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Results

Patient and graft survival

The actuarial patient survival at 1 year was 97·7 per cent. Actual survival in 73 patients followed for 1 year was 97 per cent. Two deaths have occurred, one due to pseudomonas septicaemia at 9 months and the other to a cerebrovascular accident on day 50. Actuarial graft survival, including loss from all causes (*Figure 1*) for all patients at 12, 18 and 24 months was 79·5 per cent (first graft 81·3 per cent, regraft 75 per cent). Actual graft survival, including loss from all causes, for 73 patients followed for 1 year was 77 per cent (80 per cent for 53 first graft recipients and 70 per cent for 20 regrafted patients).

The association between actuarial graft survival and matching for HLA-DR is shown for 98 cadaver graft recipients in *Figure 2* (2 donor kidneys could not be DR typed). Graft survival at 1 year and 18 months was 93 per cent in patients who received a kidney compatible for HLA-DR, compared with 83 per cent and 54 per cent, respectively, in patients receiving a kidney with one or two HLA-DR incompatible antigens ($\chi^2 = 13{\cdot}9$, d.f. = 2, $P = 0{\cdot}001$). The improvement in graft survival due to HLA-DR matching was statistically significant for first graft recipients ($\chi^2 = 7{\cdot}13$, d.f. = 2, $P = 0{\cdot}02$) and regrafted patients ($\chi^2 = 7{\cdot}99$, d.f. = 2, $P = 0{\cdot}02$). The actuarial 1 year and 18 months graft survival in 54 first graft recipients with 0 or 1 HLA-DR incompatibility was 86 per cent. Graft failure due to rejection occurred in 1 out of 29 patients who received a kidney compatible for HLA-DR, in 6 out of 47 patients who received a kidney with 1 HLA-DR incompatible antigen and in 6 out of 22 patients who received a kidney with 2 HLA-DR incompatible antigens.

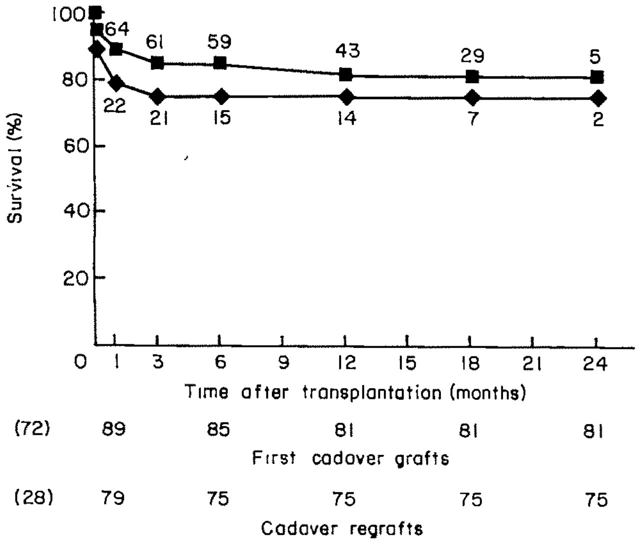

Figure 1 *Actuarial graft survival for 24 months in 100 consecutive first (■) and regrafted (◆) cadaver renal transplant recipients treated with triple therapy. Numbers on the curve indicate the number of patients at risk and numbers below the graph indicate percentage survival*

Graft function

Seventy-two grafts (72 per cent) functioned immediately. In seven patients the initial cyclosporin dose was reduced because of early non-function or a prolonged cold ischaemic time. Delayed graft function occurred in 18 grafts (18 per cent) and lasted for 14·5 ± 8 days. The total cold ischaemic time of kidneys with delayed function was significantly longer than those with primary function (27 ± 8 *versus* 22 ± 5 h, $P < 0{\cdot}01$). Primary graft function was similar in first and regrafted patients (71 *versus* 72 per cent). Permanent non-function occurred in ten grafts (10 per cent): five due to acute rejection, one due to renal artery thrombosis, one due to nephrotoxicity and three associated with renal vein thrombosis. All but one of these patients had a graft nephrectomy between the fourth and forty-fifth day

The cyclosporin dose and blood levels after transplantation are shown in *Table 1*. The cyclosporin dose at 6 months was half the initial dose and this was accompanied by a fall in the plasma and whole blood levels of cyclosporin and an improvement in renal function. Cyclosporin levels between days 1 and 7 in patients with non-functioning grafts were similar to those with functioning grafts. Higher blood cyclosporin levels were achieved more rapidly when the drug was given intravenously rather than orally, during the first

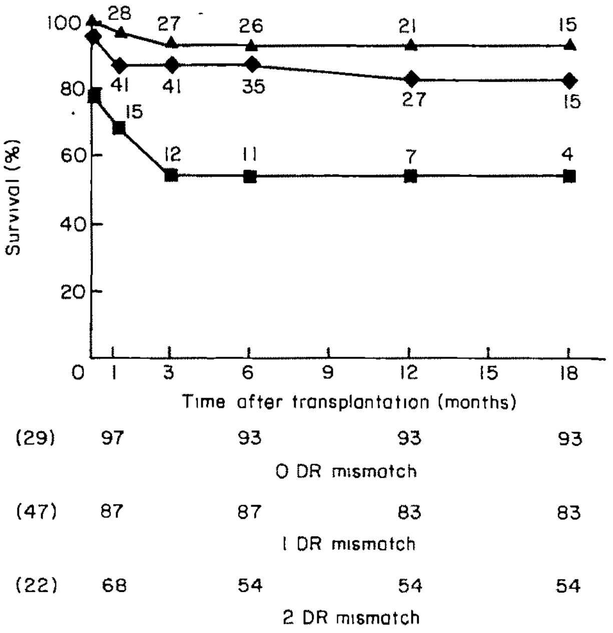

Figure 2 *Actuarial graft survival for 18 months according to HLA-DR matching in 98 consecutive cadaver renal transplant recipients treated with triple therapy (two donors could not be typed for HLA-DR)* ▲, *0 DR mismatch,* ◆, *1 DR mismatch; and* ■, *2 DR mismatches. Numbers on the curve indicate the number of patients at risk and numbers below the graph indicate percentage survival*

Table 1 *Cyclosporin dose, blood and plasma levels and serum creatinine after transplantation*

	Days after transplantation					
	7	28	90	180	365	545
CyA dose (mg kg^{-1})	9·7±1·7	9·1±2·4	6·4±2·1	4·7±1·5	4·2±1·2	4·0±1·0
CyA level plasma (ng ml^{-1})	84±77	116±85	74±72	52±33	55±29	—
CyA level whole blood (ng ml^{-1})	708±403	701±370	547±233	424±259	405±239	309±163
Serum creatinine (μmol l^{-1})	256±125	205±88	176±53	168±42	159±38	168±36

CyA, cyclosporin A. Eight patients converted from CyA were excluded after day 90. Plasma levels were used at the beginning of this study before conversion to the measurement of whole blood levels

Table 2 *Graft loss in 72 first cadaver graft recipients*

Patient	Day of graft loss	Reason for graft loss
1	3	Renal vein thrombosis
2	5	Acute rejection
3	5	Acute rejection
4	5	Renal vein thrombosis
5	5	Renal vein thrombosis
6	7	Renal vein thrombosis
7	7	Renal vein thrombosis
8	8	Nephrotoxicity
9	47	Death due to CVA
10	63	Renal artery thrombosis
11	83	Acute rejection
12	240	Chronic active rejection
13	302	Death due to sepsis

CVA, cerebrovascular accident

4 days (mean of the sum of the trough plasma cyclosporin levels between days 1 and 7 was 193±212 *versus* 76±85 ng ml^{-1}, respectively, $P<0{\cdot}001$). Only 17 per cent of patients who received oral cyclosporin exceeded the upper limit of the therapeutic range during the first week, compared with 60 per cent of patients who received intravenous cyclosporin but this had little effect on the incidence of delayed graft function (16 *versus* 20 per cent, respectively, n.s.) or the serum creatinine at 7 days (260±125 *versus* 245±110 μmol l^{-1}, respectively, n.s.). There was no correlation, in individual patients, between the dose of cyclosporin and the serum creatinine at any one point in time (7, 28, 90, 365 and 520 days) after transplantation but there was a strong linear component to the relationship between the mean serum creatinine and the mean dose of cyclosporin in grafts with stable function from 1 to 18 months after transplantation. Mean serum creatinine fell by 8 μmol l^{-1} (95 per cent confidence limits 5·5–10·5 μmol l^{-1}) for each 1 mg kg^{-1} reduction in the mean cyclosporin dosage ($P=0{\cdot}008$).

Incidence of rejection

In all, 53 of 100 graft recipients had 1 or more biopsy-proven episode of acute reversible rejection and 9 cases had biopsy-proven acute irreversible rejection within the first 90 days after transplantation. Thirty-eight transplants had no biopsy-proven rejection although six were treated for rejection on clinical criteria alone (early graft loss due to renal artery or renal vein thrombosis is included). The median time of onset for the first episode of rejection was 10 days. For all 100 grafts, the incidence of discrete episodes of rejection during the first 90 days was 0·8±0·7 per patient. This figure remains unchanged if only functioning grafts are included. Sixty-eight transplants treated for rejection in the first 90 days received 2·7±1·3 g of methylprednisolone each. For all patients, the dose of methylprednisolone given was 1·86±1·6 g per patient and this was similar for first and regraft recipients. Although matching for HLA-DR was associated with a lower incidence of acute rejection (59 *versus* 71 and 68 per cent for 0, 1 and 2 HLA-DR mismatched grafts) and less methylprednisolone (1·5±1·6 *versus* 1·7±1·5 and 2·0±1·9 g for 0, 1 and 2 HLA-DR mismatched grafts) this did not reach statistical significance. Acute rejection after day 90 has occurred in only 2 of the 100 patients who have been followed for 6 months.

A comparison between the 45 transplants who received oral cyclosporin and the 55 who received intravenous cyclosporin during the first 4 days after transplantation showed the incidence of rejection in the first 90 days was 68 and 67 per cent, respectively. The mean time of onset of rejection in the two groups was 16±15 *versus* 13±15 days, respectively. The number of grams of methylprednisolone given to patients in the two groups were 1·8±1·5 *versus* 1·9±1·7 g, respectively.

Twelve cases with biopsy-proven rejection resistant to steroids (mean dose 3·83±1·1 g) were treated with 2–4 mg kg^{-1} day^{-1} of a rabbit ATG, beginning 9–38 days after transplantation. The duration of treatment was 3–10 days with a mean of 5 days, and the mean total dose of ATG for each patient was 930±388 mg. Rejection was reversed in ten of these twelve transplants but four were subsequently treated with a further course of methylprednisolone. Graft survival in this small group was 75 per cent with a follow-up of 7·5 to 12 months, and the mean serum creatinine was 183±46, with a range of 130–251 μmol l^{-1} at their last follow-up visit.

Graft loss

Of 72 first cadaver grafts 13 (18 per cent) were lost (*Table 2*). There was a high incidence of renal vein thrombosis, four of which were associated with histological rejection. One kidney failed to function, probably due to aminoglycoside- and cyclosporin-induced nephrotoxicity. Loss from acute irreversible rejection occurred in two patients in the first week after transplantation. There was one late graft loss 83 days after transplantation when the patient stopped cyclosporin. One death occurred at day 47 after a cerebrovascular accident and another at 9 months due to septicaemia; both had functioning grafts. Of 28 regrafted patients 7 (25 per cent) lost their allograft (*Table 3*). Apart from one loss at day 0 due to a renal artery thrombosis after a cardiorespiratory arrest, the rest were due to irreversible acute rejection. Perhaps of relevance is that five of the seven failed regrafts had a positive T and B cell crossmatch in peak, but not current, sera and one patient had a positive B cell crossmatch. This high incidence of a positive crossmatch (86 per cent) however, was not significantly different from that seen in the successful regrafts where 11 out of 21 (52 per cent) had a positive crossmatch ($\chi^2=2{\cdot}45$, d.f.=1, n.s.). Overall, nine of the twenty grafts were lost as a result of acute irreversible rejection, one with no HLA-DR mismatch, two with one mismatch and six with two mismatches.

Nephrotoxity

Acute nephrotoxicity was uncommon. In 13 transplants patients had an acute rise of serum creatinine (>20 per cent within a period of 7 days) which was treated successfully by a dose reduction of cyclosporin. Nephrotoxicity was not a clinical problem in the early post-transplant period and occurred at a mean of 51 (s.d.=35) days after transplantation. There was no obvious relationship between nephrotoxicity and the trough cyclosporin levels. This low incidence of toxicity was probably due to the progressive reduction in cyclosporin dosage according to protocol. However, serum creatinine remained above the upper limit of normal at 6 and 12 months.

Leucopenia

Twenty-eight per cent of patients with a functioning graft developed leucopenia (white blood cell count $<4\times10^3$ mm^{-3}) requiring a reduction in azathioprine dosage between 17 and 70 days after transplantation. Leucopenia or pancytopenia developed within 21 days of the start of treatment in nine of the twelve patients who received ATG and two of these patients with severe anaemia required transfusion. All responded to a reduction in dosage of azathioprine and the drug was stopped in only one patient because of the development of haemolytic anaemia.

Table 3 *Graft loss in 28 regrafted patients*

Patient	Day of graft loss	Reason for graft loss
1	0	Renal artery thrombosis
2	0	Accelerated rejection
3	0	Accelerated rejection
4	4	Acute rejection
5	12	Acute rejection
6	28	Acute rejection
7	83	Acute rejection

Table 4 *Infectious complications requiring admission to hospital in 100 consecutive cadaver renal transplants*

Major	*n*	Minor	*n*
Pneumocystis carinii pneumonia	3	Cytomegalovirus	6
Cytomegalovirus	3	Urinary tract infection	2
Bacterial septicaemia	2	Perianal abscess	2
Pneumonia bacterial and viral	2	Bronchitis	1
Herpes zoster	2	Pyrexia unknown origin	1
Epididymo-orchitis	2	Diarrhoea and vomiting	1
Wound infection	1		
Urinary tract infection	1		
Pulmonary tuberculosis	1		
Pyrexia unknown origin	1		

n, Number of patients

Infection

Thirty-one patients were re-admitted to hospital with infectious complications. Eighteen were classified as serious and thirteen as minor (*Table 4*). Of the first 25 patients, 3 developed pneumocystis carinii pneumonia between 70 and 130 days after transplantation. All survived with functioning grafts. There were no further cases after the introduction of prophylactic cotrimoxazole, one tablet daily (80 mg trimethoprim, 400 mg sulphamethoxazole) for 6 months. Nine patients were admitted to hospital with cytomegalovirus (CMV) infection but only three had a serious illness; five were primary infections and four were due to re-activation. Symptomatic cytomegalovirus infection occurred in five other patients who did not require admission. One death occurred from pseudomonas septicaemia. Wound infections occurred in three patients.

Complications

Other complications included the development of a lymphocele in two patients, an incisional hernia in one patient, renal artery stenosis requiring correction in two patients, and one case of ureteric stenosis requiring implantation of the ureter 6 months after transplantation.

Conversion

Cyclosporin was stopped in eight patients between day 90 and 140. This was because of hirsutism in five female patients, poor renal function in two patients and persistent pneumocystis carinii infection in one patient. Three of these eight patients developed acute rejection within 40 days of conversion, two of whom responded to the re-introduction of cyclosporin and the other to steroids. No grafts were lost.

Discussion

Triple therapy is being widely used as the primary form of immunosuppression in renal transplantation. Initial fears about the safety of the regimen[15] have not been confirmed in this or other studies[2,16,17]. One year graft and patient survival in first and regrafted patients treated with triple therapy in the Oxford transplant unit, compares favourably with patients treated in the same unit with cyclosporin and conversion to azathioprine and prednisolone at 90 days[18]. Excellent graft survival has been confirmed in other centres using triple therapy protocols[2,12,13,16,19]. Furthermore, there was a strong influence of matching for HLA-DR on graft survival in this analysis, comparable to that seen previously in this unit in patients treated with azathioprine and prednisolone[20,21]. The role of matching for HLA in general and HLA-DR in particular is controversial in patients receiving cyclosporin but it should be emphasized that the reproducibility of typing for HLA-DR is not optimal in many units and this may explain the lack of correlation between graft outcome and matching for HLA-DR in some reports[22].

In this study infectious complications were not a major problem in most patients although 35 per cent of 89 patients with functioning grafts were re-admitted to hospital for infection. A similar incidence has been reported from other centres using triple therapy[3,13,16] Severe sepsis and death occurring during immunosuppression with triple therapy regimens has been associated with the prolonged use of ATG or antilymphocyte globulin[3,16]. Our experience would also confirm that there is an increased risk of symptomatic cytomegalovirus infection in the subgroup of triple therapy patients treated with ATG (33 *versus* 12 per cent in those not given ATG). Although the occurrence of three cases of pneumocystis carinii pneumonia in these patients was worrying, the introduction of prophylactic co-trimoxazole for 6 months after transplantation appears to have prevented the development of any further cases, either in this series or subsequently.

Signs of rejection were attenuated in patients receiving triple therapy and the diagnosis was often difficult to make on clinical grounds. Although we depended heavily on percutaneous biopsy and graft histology to diagnose rejection, cellular infiltrate was common[23] and often difficult to correlate with renal function. Triple therapy was associated with a reduction in the incidence of acute rejection and in the requirement for methylprednisolone during the first 90 days when compared with patients in this unit treated with cyclosporin alone (1·8 ± 1·6 g methylprednisolone per patient *versus* 2·7 ± 1·3 g methylprednisolone per patient, respectively, $P<0{\cdot}01$)[18]. However, the two groups were not fully comparable since in the triple therapy group the percentage of patients with panel reactive antibodies was less and the percentage with deliberate or random transfusion before transplantation was greater than in the cyclosporin alone group. The lower incidence of acute reversible rejection reported with triple therapy in Minneapolis[2] (31 per cent in the first 12 months *versus* 53 per cent in the first 3 months in the Oxford series) was probably due to the routine use of prophylactic antilymphocyte globulin during the first 7–14 days in that centre.

Primary graft function (72 per cent) was similar to that of Minneapolis (62 per cent) where the introduction of cyclosporin was delayed until the fifth day[2]. Because of a delay in achieving adequate early blood levels with oral cyclosporin, the drug was given intravenously during the first 4 days for the latter half of the study period. Although higher blood levels were achieved more rapidly within the first 7 days with intravenous compared with oral administration, the incidence of delayed graft function was not significantly different and renal function was similar at 7 days. There was no obvious difference in the incidence of early rejection, graft loss or vascular thrombosis between the groups.

An increased incidence of renal artery and renal vein thrombosis has been reported with the use of cyclosporin[9,24,25]. Our experience with low-dose cyclosporin in conjunction with azathioprine and prednisolone confirms this finding, which is of considerable concern when seen in the light of our total experience of only one case each of renal artery and renal vein thrombosis in 365 renal allograft recipients immunosuppressed with azathioprine and prednisolone.

Triple therapy has maintained the immunosuppressive advantages of high-dose cyclosporin in first and regrafted cadaver renal allograft recipients. There was no evidence that patients had been over immunosuppressed. Acute nephrotoxicity was uncommon and rarely a clinical problem with the progressive reduction in cyclosporin dose. Despite lower doses of the drug renal function remained suboptimal at 6 and 12 months but was similar to that reported with low-dose cyclosporin alone[26] and other triple therapy regimens[12]. Experimental evidence in the animal model suggests there is a synergistic immunosuppressive effect between cyclosporin and azathioprine[27]. Whether protocols of low-dose cyclosporin alone or in combination with low-dose steroids, or cyclosporin conversion protocols are as effective as triple therapy is uncertain, as too is the question of whether one or even two drugs might be discontinued from the triple therapy regime after a period of time. The answers to these questions will only be provided by large multicentre controlled trials. Triple therapy is an effective immunosuppressive regimen in the short-term and there appears to be a strong influence on graft survival of matching for HLA-DR.

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Recurrence of varices after oesophageal transection: intra-operative and postoperative assessment by endoscopy

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Intra-operative and postoperative endoscopy were used in 16 patients with portal hypertension to investigate whether intra-operative elimination of oesophageal varices by oesophageal transection with devascularization leads to prevention of variceal recurrence and rebleeding. Intra-operative elimination of the varices was achieved in 12 patients. In ten patients the varices recurred and in two cases rebled, during the follow-up period of 6–43 months (average 25 months). Of the ten patients with recurrent varices, eight (including the two who bled acutely in the postoperative period) successfully underwent endoscopic injection sclerotherapy. Postoperative endoscopy was performed at 5-monthly intervals. It is concluded that intra-operative elimination of the varices will not prevent recurrence and that a closer follow-up using endoscopy more than three times a year is a significant aid in the management of these patients.

Keywords: Oesophageal varices, oesophageal transection, endoscopy, endoscopic injection sclerotherapy

Postoperative variceal recurrence and rebleeding remain serious complications of the surgical treatment of oesophageal varices. After shunt operations, occlusion of the venous anastomosis is the main cause of recurrence of varices and such failure may occur in the early postoperative period[1]. In the case of direct interruption procedures, the incidence of postoperative variceal rebleeding seems to increase with the passage of time[1]. Although the mechanisms involved in variceal recurrence after direct interruption procedures remain obscure, remnant varices which result from insufficient devascularization around the oesophagus and the upper stomach may be a cause of variceal recurrence and rebleeding. Yamamoto *et al.*[2] have reported that intra-operative endoscopy is a useful means of ensuring sufficient devascularization.

The objective of the present study was to investigate whether confirmation of elimination of the varices by intra-operative endoscopy could prevent variceal recurrence and rebleeding in patients undergoing direct interruption procedures.

Patients and methods

From April 1982 to December 1984, 20 Japanese patients with endoscopically documented oesophageal varices underwent an oesophageal transection using an EEA stapling device (United States Surgical Corp.) in the Department of Surgery II, Kyushu University Hospital. The patients comprised 17 men and 3 women, aged from 34 to 64 years (mean 47 years). Fifteen had a history of bleeding: Child's classification was evaluated as A in five, B in eleven and C in four. During each operation, intra-operative endoscopic examination (GIF-P2, Olympus) was performed and alterations in the oesophageal varices were sequentially assessed at the beginning of laparotomy, after splenectomy, after initial ordinary devascularization, and again after clamping of the oesophagogastric junction, using intestinal forceps, to represent an oesophageal transection. In the usual devascularization procedures after splenectomy, the left gastric vessels were divided at the superior border of the pancreas and the proximal half of the stomach was entirely denuded by dissection of the left gastric, the left gastro-epiploic and the short gastric vessels. The abdominal oesophagus was also denuded and truncal vagotomy was performed with pyloroplasty. When remnant varices were endoscopically observed, even after clamping of the oesophagogastric junction, an extensive devascularization was added and consisted of dissection of the posterior gastric veins and isolation of the lower mediastinal oesophagus through the hiatus. Thereafter, endoscopic examination was repeated with clamping of the junction. The oesophagus was finally transected 2 cm above the junction.

Of the 20 patients so treated, 3 cirrhotics died and 1 with prehepatic portal obstruction was lost to follow-up within 6 months of operation. The remaining 16 patients included in the present study were followed by periodic oesophageal endoscopy. There were 13 men and 3 women ranging in age from 34 to 64 years (mean 48 years). Of 16 patients, 12 experienced one or more episodes of haemorrhage. The liver diseases of the patients included non-alcoholic cirrhosis in 13 and prehepatic portal obstruction in 3; the hepatic reserve was classified as Child's A in 4, B in 8 and C in 4.

The oesophageal endoscopy was carried out by one of three surgeons in our department and findings of the varices were confirmed by at least two of them. The findings were documented according to the general rules for recording endoscopic findings of oesophageal varices proposed by the Japanese Research Society for Portal Hypertension[3]. In the present study, postoperative recurrence of the oesophageal varices was defined as moderate-sized (F2) and/or red colour signs positive, as noted at a follow-up endoscopy performed every 3–6 months.

Statistical analysis was made using the χ^2 test with Yates's correction.

Results

Intra-operative endoscopy

Endoscopic findings after each stage of the operative procedure are summarized in *Table 1*. A decrease in size of the varices after ordinary devascularization was noted in only three patients with prehepatic portal obstruction. Even after the oesophageal clamping, small varices (F1) remained in 12 patients, and extensive devascularization resulted in elimination of the varices in 8 of these.

Red colour signs disappeared in half of the patients after the usual devascularization and were eliminated in all by transection of the oesophagus.

Postoperative recurrence and rebleeding

Sixteen patients were followed for 6–43 months (mean 25 months) during which 79 endoscopic examinations were carried

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Table 1 *Endoscopic findings of oesophageal varices after each operative procedure in 16 patients*

	Variceal form				Red colour signs	
	F3	F2	F1	(−)	(+)	(−)
Pre-operative	11	5	0	0	16	0
Ordinary devascularization	9	4	3	0	8	8
OGJ clamping*	0	0	12	4	0	16
Extensive devascularization	0	0	4	12	0	16

*OGJ (oesophagogastric junction) clamping is comparable to the oesophageal transection procedure

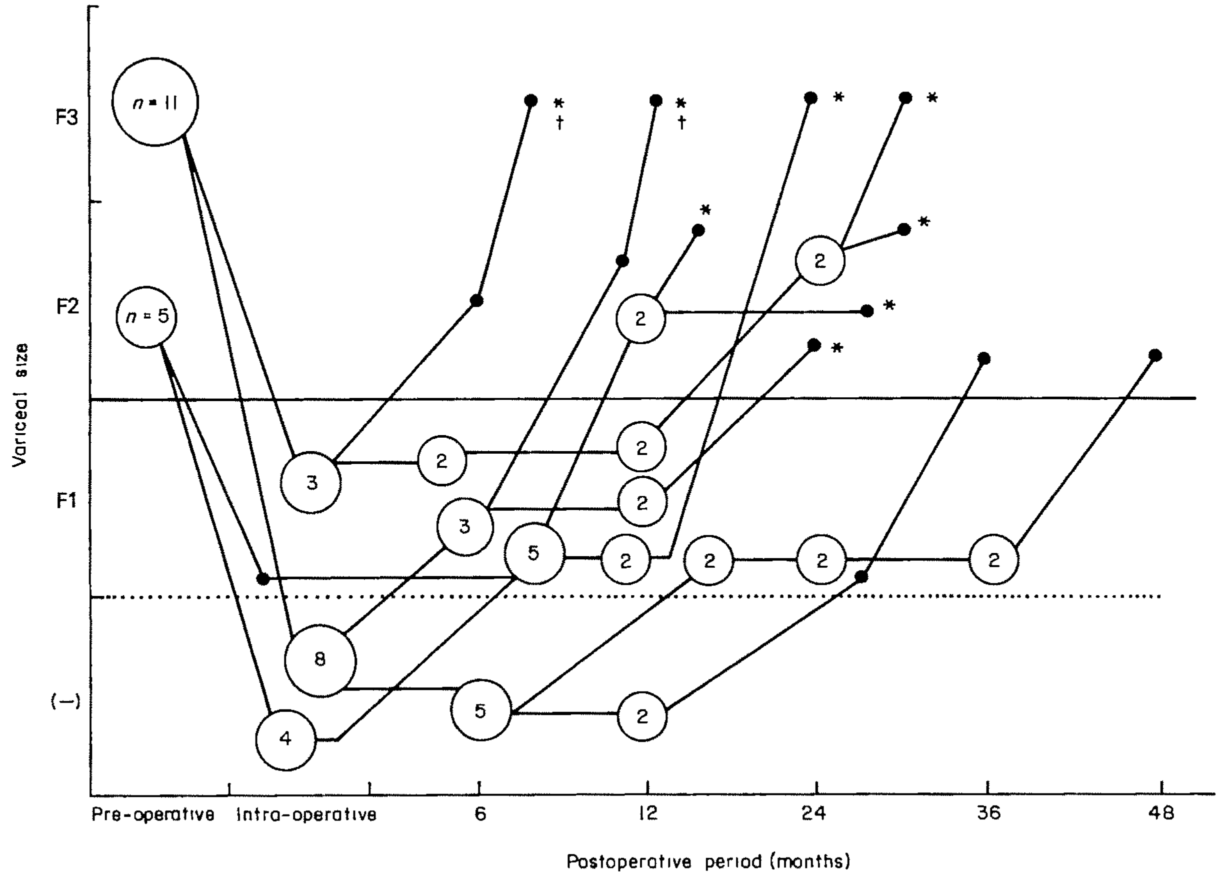

Figure 1 *Postoperative endoscopic findings with regard to variceal size (F3, large, F2, moderate and F1, small) in each patient. * Eight patients underwent endoscopic injection sclerotherapy using 5 per cent ethanolamine oleate with good results, †occurrence of bleeding; ●, indicates an individual patient. There was a recurrence of F2- or F3-sized varices in ten patients including two who bled*

out. The mean interval between endoscopies was 5 months per patient. Variceal recurrence was noted in 10 of 16 patients (62·5 per cent) at 3–36 months, with an average of 16 months. There was no significant difference in the recurrence rate of varices between the 12 patients with operative variceal elimination (50·0 per cent) and the 4 with remnant small varices (100 per cent) ($\chi^2 = 1{\cdot}422$, $P < 0{\cdot}20$).

Of the 10 patients with recurrent varices, 2 rebled at the eighth and thirteenth month postoperatively, respectively. Each variceal haemorrhage was successfully controlled by emergency endoscopic injection sclerotherapy (EIS) using 5 per cent ethanolamine oleate. Eight patients with a recurrence, including the two patients who bled, were treated by EIS 8–28 months postoperatively (average of 20 months). *Figure 1* shows the postoperative course with regard to the endoscopic findings of variceal size in each patient. The cumulative recurrence rates of oesophageal varices were 12·1, 31·0, 57·3 and 63·4 per cent at 6, 12, 24 and 36 months postoperatively.

Discussion

Oesophageal endoscopy is an important tool in the management of patients with portal hypertension and oesophageal varices. In 1980, the Japanese Research Society for Portal Hypertension proposed a general rule for recording endoscopic findings of the oesophageal varices, to assure an objective evaluation of variceal appearance[3]. On the basis of these rules, we reported that the fundamental blue colour in varices of more than moderate size (F2 and F3) and the red colour signs were predictive of variceal haemorrhage[4]. Oesophageal varices with such endoscopic findings (blue colour and/or red colour signs) were likely to bleed, and the 2-year cumulative bleeding rate in non-surgical patients was 31·6 per cent in a prospective trial[5].

The efficacy of surgical treatments in prevention of variceal rebleeding has been evaluated by the rebleeding rate; however, the recurrence rate of the varices should also be taken into account. To our knowledge, data based on a close follow-up study of the oesophageal varices by endoscopy and assessment of variceal recurrence after surgery have not been reported.

Among various methods used to treat oesophageal varices, transection of the oesophagus combined with Hassab's method[6], including splenectomy and devascularization of the oesophagogastric junction, is in worldwide use, probably due to the time-saving introduction of the EEA stapler[6–8]. The rebleeding rate, however, was reported as ranging from 6 to

25 per cent[9–13]. A nationwide survey of Japanese patients treated by oesophageal transection revealed that a cumulative rebleeding rate was around 20 per cent at the tenth postoperative year[1]. We therefore set out to determine whether recurrence of oesophageal varices after direct interruption, in which portal hypertension remains, may be inevitable.

Yamamoto *et al.*[2] reported the intra-operative use of endoscopy to assure sufficient devascularization in their operation of cardia resection. To clarify whether extensive devascularization could eliminate the varices, and to assess whether intra-operative elimination prevents postoperative variceal recurrence and rebleeding, we used intra-operative endoscopic examinations during our operation of trans-abdominal oesophageal transection with Hassab's devascularization[6]. The usual devascularization did not lead to complete collapse of the varices, but there was a minimal change in their form (three patients) and red colour signs (eight patients). Elimination followed transection in only four patients. After additional devascularization of the posterior gastric vein and the lower mediastinal oesophagus, the oesophageal varices were eliminated in eight patients. Thus, oesophageal transection with extensive devascularization eliminated the varices in 12 of 16 patients. The remnant varices in the remaining four underline the importance of intrathoracic feeding routes, such as the oesophageal arteries and veins.

Postoperative follow-up with periodic endoscopy revealed a high recurrence rate of 62·5 per cent at a mean of 16 months postoperatively and rebleeding occurred in 12·5 per cent of patients. The recurrence of oesophageal varices increased with the passage of time, as previously suggested by a constant increase in the postoperative bleeding rate of patients after oesophageal transection[1]. It was thus concluded that intra-operative elimination of the varices by oesophageal transection even when combined with extensive devascularization will not prevent postoperative recurrence and rebleeding in patients with portal hypertension and oesophageal varices.

Such clinical results also suggest the importance of postoperative follow-up by periodic endoscopy for early detection of variceal recurrence and to allow treatment of the recurring varices. In the early stage of the present study, two patients had postoperative bleeding which was controlled by emergency EIS. Thereafter, we shortened the interval of endoscopic examinations from every 5–6 months to every 3–4 months, and began EIS for patients who developed recurrent varices of moderate (F2) to large (F3) size with blue colour and/or red colour signs. We still consider that EIS is the treatment of choice for patients with recurrence of oesophageal varices[14].

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Results of resection of gastric cancer extending to adjacent organs

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We report the late results of resection in 281 patients with gastric carcinoma extending to adjacent organs. In 92 without incurable factors (peritoneal dissemination, liver metastasis and widespread nodal involvement) the 5-year survival rate was 36·7 per cent in those treated by gastrectomy and complete removal of the invaded organ. This value is significantly higher than the 17·4 per cent recorded in those undergoing gastrectomy alone or with incomplete removal of the invaded organs ($\mathrm{P}<0{\cdot}05$)*. In 189 patients with incurable factors, the 5-year survival rates were 5·4 and 2·8 per cent respectively in cases of complete and incomplete excisions. This tendency was similar in patients with a single invaded organ and also in those with plural organ involvement. In potentially curable patients treated by complete excision, the probability of long-term survival was statistically better than that following incomplete excision only when the pancreas was involved* ($\mathrm{P}<0{\cdot}05$)*. We recommend complete excision of invaded organs, irrespective of the number or site of organs involved, provided that there is no evidence of incurable factors.*

Keywords: Gastric carcinoma, survival, combined resection

Although in the majority of patients with gastric carcinoma the primary lesion is confined to the gastric wall, in about 10 per cent of resected patients, the tumour crosses the serosal layer and extends to adjacent organs[1,2]. In such cases, others have suggested the need for extensive *en bloc* resection of the invaded organs[3–5]. However, patients with tumours extending to adjacent organs frequently have factors apparent at laparotomy (including peritoneal dissemination, liver metastasis and widespread nodal involvement) which indicate incurability[6]. Therefore, intra-operative assessment of tumour spread plays a critical part in defining the extent of surgical excision in attempts to lengthen survival for patients with advanced gastric carcinoma.

We have reviewed our experience with such patients, with special emphasis on the combined resection of stomach with invaded organs.

Patients and methods

Of 1262 Japanese patients with gastric carcinoma who had undergone resection in the Department of Surgery II, Kyushu University Hospital from 1964 to 1978, there were 281 (22·3 per cent) with tumour extending to adjacent organs. The invasion was macroscopically defined at laparotomy and the organs invaded are listed in *Table 1* There were 129 patients (45·9 per cent) who underwent gastrectomy combined with complete removal of the invaded organs (complete excision) and 152 (54·1 per cent) who were treated by gastrectomy alone or gastrectomy with incomplete removal of invaded organs (incomplete excision); there were 4 (3·1 per cent) operative deaths (within 1 month) in the former patients and 4 (2·6 per cent) in the latter.

These 281 patients were classified into two groups according to whether there was evidence of prognostic factors (incurable factors) such as peritoneal dissemination, liver metastasis and widespread nodal involvement. Group A included 92 patients with neither peritoneal dissemination nor liver metastasis, for whom gastrectomy with sufficient lymphadenectomy of primary, secondary and/or tertiary nodes[1,2] had been performed. Group B consisted of 189 patients with peritoneal dissemination, liver metastasis and lymphadenectomy which was deemed insufficient because of widespread nodal involvement extending to tertiary (hepatoduodenal, retropancreatic or mesenteric) or quaternary (middle colic or para-aortic) nodes[1,2], either alone or in various combinations.

Groups A and B were further divided into two subgroups, according to the extent of surgical excision: namely, complete and incomplete excisions. Clinical data from each group are shown in *Table 2*. In group A, there were no statistical differences between complete and incomplete excision patients, while in group B, a statistical difference was evident between the two subgroups, with regard to type of gastrectomy and nodal involvement.

Table 1 *Invaded organs in 281 patients*

Organs invaded	No. of of patients	Patients with combined resection
One organ		
Pancreas	96	47 (49·0)*
Mesocolon	64	37 (57·8)
Peritoneum†	21	3 (14·3)
Liver	14	9 (64·3)
Colon	12	10 (83·3)
Total	207	106 (51·2)
Two organs		
Pancreas + mesocolon	28	6 (21·4)
Pancreas + colon	16	7 (43·8)
Pancreas + peritoneum†	4	1 (25·0)
Pancreas + liver	3	3 (100)
Others‡	11	4 (36·4)
Total	62	21 (33·9)
Three organs		
Pancreas + mesocolon + liver	3	1 (33·3)
Others‡	8	1 (12·5)
Total	11	2 (18·2)
Four organs		
Pancreas + colon + spleen + retroperitoneum	1	0
Total	281	129 (45·9)

* Numbers in parentheses indicate the percentage of patients in whom combined resection of the invaded organ was performed †Peritoneum included that lining the abdominal wall, retroperitoneum and diaphragm. ‡Combination groups comprising fewer than two cases were included in 'Others'

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Table 2 *Clinical data of study patients*

Factors	Group A Complete excision	 Incomplete excision	Group B Complete excision	 Incomplete excision
Number of patients	68	24	61	128
Mean age	57·4	57·3	53·9	54·9
Sex				
Male	53 (77·9)†	20 (83·3)	44 (72·1)	79 (61·7)
Female	15 (22·1)	4 (16·7)	17 (27·9)	49 (38·3)
Type of histology‡				
Differentiated	29 (42·6)	9 (37·5)	23 (37·7)	51 (39·8)
Undifferentiated	32 (47·1)	13 (54·2)	30 (49·2)	70 (54·7)
Others	7 (10·3)	2 (8·3)	8 (13·1)	7 (5·5)
Type of gastrectomy				
Total	37 (54·4)	10 (41·7)	45 (73·8)**	63 (49·2)
Distal partial	29 (42·6)	14 (58·3)	13 (21·3)	64 (50·0)
Others	2 (3·0)	0	3 (4·9)	1 (0·8)
Nodal involvement				
None (n0)	17 (25·0)	8 (33·3)	1 (1·6)	10 (7·8)
Primary (n1)	21 (30·9)	6 (25·0)	9 (14·8)	11 (8·6)
Secondary (n2)	26 (38·2)	7 (29·2)	23 (37·7)	24 (18·8)
Tertiary (n3)	4 (5·9)	3 (12·5)	13 (21·3)	45 (35·2)
Quaternary (n4)	0	0	15 (24·6)	38 (29·6) *

†Numbers in parentheses are percentages. There is a statistical difference compared with complete excision (*$P<0·05$), and compared with incomplete excision (**$P<0·01$). ‡Differentiated type of adenocarcinoma includes well and moderately differentiated adenocarcinomas while undifferentiated type adenocarcinoma includes poorly differentiated adenocarcinoma and signet ring cell carcinoma

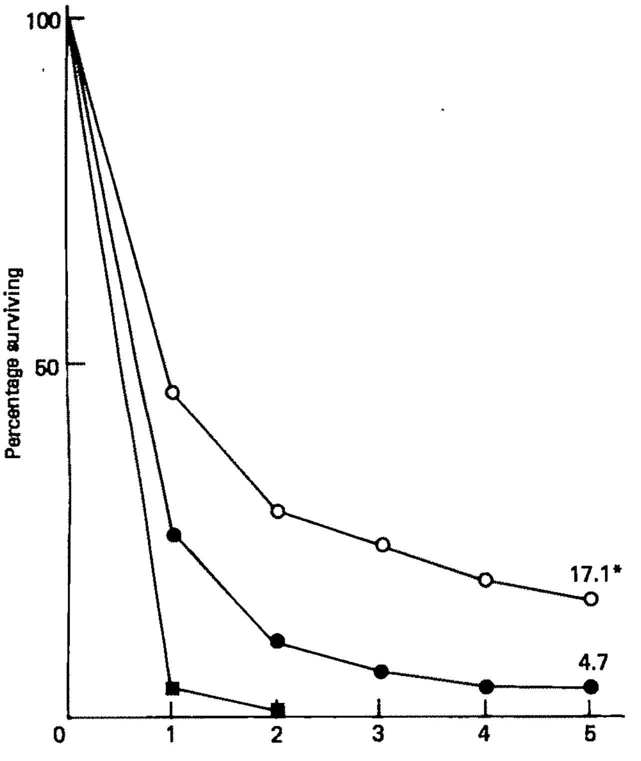

Figure 1 *Survival of patients with involvement of one* (○, n = *207*), *two* (●, n = *62*) *or more than three* (■, n = *12*) *organs.* **Statistically significant difference compared with two-organ involvement* ($P<0·01$ *by Wilcoxon test*)

The survival rates were calculated by actuarial methods and statistical analyses of the survival rates were made using the Wilcoxon test and/or the Mantel–Haenzel test

Results

Figure 1 shows the survival curves of patients with different numbers of invaded organs. The 5-year survival rate in patients with a single invaded organ was 17·1 per cent, this being significantly higher than the 4·7 per cent observed in those with two invaded organs ($P<0·01$). In 207 patients with a single invaded organ, 77 (37·2 per cent) were classed as group A and 130 (62·8 per cent) were in group B. Patients (62) with 2 invaded organs consisted of 14 (22·5 per cent) in group A and 48 (77·4 per cent) in group B. Eleven of twelve (91·7 per cent) with over three organs involved belonged to group B. Thus, about 80 per cent (59/74) of patients with tumour extending to more than two organs were classed in group B as opposed to 62·8 per cent (130/207) of those with a single invaded organ ($P<0·01$).

The results with regard to site of invaded organs are shown in *Table 3*. There was a relatively favourable prognosis in patients with mesocolon involvement with a 5-year survival rate of 24·6 per cent. The 5-year survival rates were 17·2, 15·4, 12·9 and 9·8 per cent respectively, in cases with involvement of peritoneum, liver, pancreas and colon.

Complete excision was carried out in 68 (73·9 per cent) and 61 (32·3 per cent) patients in groups A and B respectively. In group A, the extent of excision appeared to influence the survival in patients with a single invaded organ, and also in those with multiple organ involvement. The overall 5-year survival rate was 36·7 per cent in patients who had undergone complete excision, which was significantly higher than the 17·4 per cent in those undergoing incomplete excision ($P<0·05$) (*Table 4*). In group B, the overall 5-year survival rates were 5·4 per cent and 2·8 per cent in cases of complete and incomplete excisions respectively. There was no significant difference between the two subgroups. A similar tendency was observed in patients with a single invaded organ, and in those with plural organ involvement (*Table 5*).

The probability of survival for group A patients was further studied from the standpoints of site of organ and extent of excision (*Table 6*). Complete excision led to a significant chance of long-term survival in those with invasion limited to the pancreas. The differences in survival rates were statistically significant at the first and second postoperative years in favour of those with complete excision ($P<0·05$). Relatively favourable results were observed in those undergoing complete excision of tumour invading peritoneum, liver, colon and pancreas plus mesocolon or colon. Of three patients with invasion of the diaphragmatic peritoneum, one survived over 5 years and two died of causes not related to gastric carcinoma.

Table 3 *Survival in terms of site of organ invaded*

Site of organs	Number of cases*	Survival rates (%) 1-year	2-year	3-year	4-year	5-year
One organ						
Mesocolon	64	59·1	39·6	31·4	26·4	24·6
Peritoneum†	21	36·8	28·7	28·7	17·2	17·2
Liver	14	30·8	30·8	15·4	15·4	15·4
Pancreas	96	42·9	26·0	21·8	17·4	12·9
Colon	12	39·1	9·8	9·8	9·8	9·8
Two organs						
Pancreas + mesocolon	28	24·5	9·8	4·9	—	—
Pancreas + colon	16	24·1	—	—	—	—

* Combination groups comprising fewer than ten patients were not included. † Peritoneum included that lining the abdominal wall, retroperitoneum and diaphragm

Table 4 *Survival in terms of type of excision (Group A)*

Type of excision	Number of cases	Survival rates (%) 1-year	2-year	3-year	4-year	5-year
One organ						
Complete	57	78·2**	66·5**	54·2	41·7	39·5
Incomplete	20	48·7	32·5	32·5	27·1	21·1
Two organs						
Complete	11	42·9	21·4	21·4	21·4	21·4
Incomplete	3	33·3	—	—	—	—
Over three organs						
Complete	0	—	—	—	—	—
Incomplete	1	—	—	—	—	—
Total						
Complete	68	72·5	59·3	49·0	38·5	36·7*
Incomplete	24	44·7	26·8	26·8	22·3	17·4

There is a statistical difference compared with incomplete excision (*$P<0·05$, Wilcoxon test; **$P<0·01$, Mantel–Haenzel test).

Table 5 *Survival in terms of type of excision (Group B)*

Type of excision	Number of cases	Survival rates (%) 1-year	2-year	3-year	4-year	5-year
One organ						
Complete	49	30·5	10·2	10·2	10·2	6·8
Incomplete	81	32·9	12·7	7·2	7·2	4·3
Two organs						
Complete	10	22·2	22·2	22·2	—	—
Incomplete	38	21·1	8·5	—	—	—
Over three organs						
Complete	2	—	—	—	—	—
Incomplete	9	5·9	—	—	—	—
Total						
Complete	61	28·2	10·8	10·8	8·1	5·4
Incomplete	128	27·5	10·7	4·7	2·8	2·8

Discussion

With advances in surgical technique and postoperative care, there has been a remarkable reduction in the operative mortality for patients with gastric carcinoma[5,7]. In our institute of the 129 patients who underwent gastrectomy plus complete removal of invaded organs, operative deaths amounted to four deaths (3·1 per cent), the mortality rate being similar to that following gastrectomy alone or gastrectomy with incomplete removal of the invaded organs.

In our study of the prognosis of advanced gastric carcinoma[6], we found that direct invasion to adjacent organs was not an indicator of incurability when compared with factors such as peritoneal dissemination, liver metastasis and quaternary nodal involvement. About 20 per cent of patients with tumour extending to adjacent organs alone survived 5 years after gastrectomy (with or without combined resection of the invaded organs)[6]. At the time of laparotomy, determining the extent of surgical excision may present a problem when there is carcinoma invading adjacent organs plus evidence of metastatic spread.

In the current study, we found that extension of tumour beyond a single organ significantly reduced the resectability rate and survival time because of the frequency of various incurable factors other than direct invasion to adjacent organs.

Table 6 *Survival in terms of type of excision (Group A)*

Type of excision	Number of cases†	Survival rates (%)				
		1-year	2-year	3-year	4-year	5-year
Pancreas						
Complete	19	83·8*	72·2*	59·7	39·8	33·1
Incomplete	11	45·5	27·3	27·3	27·3	18·2
Mesocolon						
Complete	27	77·8	66·4	54·7	43·0	43·0
Incomplete	4	50·0	50·0	50·0	50·0	50·0
Peritoneum‡						
Complete	3§	100	100	100	100	100
Incomplete	3	66·7	33·3	33·3	—	—
Liver						
Complete	4	50·0	50·0	25·0	25·0	25·0
Incomplete	2	33·3	—	—	—	—
Colon						
Complete	4	71·4	35·7	35·7	35·7	35·7
Incomplete	0	—	—	—	—	—
Pancreas + mesocolon						
Complete	4	25·0	—	—	—	—
Incomplete	2	—	—	—	—	—
Pancreas + colon						
Complete	4	50·0	—	—	—	—
Incomplete	0	—	—	—	—	—

* There are statistical differences compared with incomplete excision ($P<0·05$ by Mantel–Haenzel test). † Combination groups comprising a single patient were not included. ‡ Peritoneum included that lining abdominal wall, retroperitoneum and diaphragm § One of three patients with diaphragm invasion survived 5 years

Nevertheless, complete removal of invaded organs proved to be worthwhile even in patients with multiple organ involvement and in those with a single organ involvement, when peritoneal dissemination, liver metastasis and widespread nodal involvement were not evident at operation. On the other hand, in the presence of such factors, extensive procedures did not prolong the survival time, regardless of the number of organs invaded. These findings suggest that the effectiveness of complete excision is related not so much to multiple organ involvement as it is to the presence of incurable factors. Further analysis of the prognosis in the potentially curable patients (group A) indicates that complete excision is essential to prolong survival, especially in those with invasion limited to the pancreas. Similar findings were observed in cases with spread to the diaphragm, liver and colon. Kishimoto and Koga[5] reported an unfavourable prognosis in patients with tumour invading the transverse colon and in those who underwent gastrectomy plus colectomy, compared with those undergoing combined resection of pancreas or liver. In their series, only one of 12 patients survived 5 years[5] whereas we obtained a 5-year survival rate of 35·7 per cent in those undergoing complete excision for the tumour invading the transverse colon, a rate similar to that in cases with invasion to pancreas, mesocolon and liver. Although this is encouraging, it must be stressed that the number of patients was small.

In the light of all the previous findings in the past years, our present policy is to undertake gastrectomy with complete removal of any invaded organs when a curative operation seems feasible. When the surgery is palliative due to the presence of various incurable factors, gastrectomy still seems preferable to laparotomy alone or gastrojejunostomy, because symptoms were alleviated and the survival time was prolonged as usually reported[8–10].

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Surgical management of bleeding gastric ulceration

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In a nine-year period from 1977 to 1985 sixty-one patients underwent surgery for bleeding gastric ulceration in the Western Infirmary, Glasgow. Nineteen patients were treated by partial gastrectomy, twenty-two had undersewing of the ulcer plus vagotomy and drainage and twenty had undersewing alone. Mortality in the three groups was 26, 45 and 10 per cent respectively. All groups of patients were similar in terms of age, severity of haemorrhage, delay before surgery and grade of surgeon performing the procedure. Out-patient follow-up (mean: 37 months) of patients treated by undersewing alone revealed that 73 per cent were symptom free. Treatment of bleeding gastric ulceration by undersewing alone is effective and should be considered in patients who require surgery.

Keywords: Gastrectomy, peptic ulcer haemorrhage, vagotomy

The management of patients with acute upper gastrointestinal haemorrhage from peptic ulceration has received considerable attention in recent years. Much of the clinical research and resulting debate has centred on whether medical or surgical management is more appropriate and how best these two treatment options can be integrated[1–3]. The importance of identifying patients at high risk of rebleeding from their ulcers has been recognized and discussion has focused on the optimum timing of surgery in this group of patients[4–6]. While these aspects of surgical practice have received much attention, little consideration has been given to the surgical procedure that should be carried out once the decision to operate has been made.

In patients with bleeding gastric ulceration the traditional approach has been to perform a partial gastrectomy[7]. The high mortality associated with emergency gastrectomy in the elderly prompted some surgeons to adopt a more conservative approach consisting of undersewing of the ulcer combined with truncal vagotomy and drainage[8,9]. Both these approaches to the treatment of haemorrhage from gastric ulceration combine haemostasis with surgery to prevent ulcer recurrence. With the advent of effective anti-ulcer drugs over the last decade, the need to perform an ulcer-healing operation at the time of surgery for haemorrhage control may well have been abolished in all but a very few patients. Consequently some surgeons have adopted a policy of undersewing alone to achieve haemostasis in bleeding gastric ulceration. This trend, from more extensive procedures towards conservative surgery, has been apparent in the practice of the surgeons in the Haematemesis Management Team at the Western Infirmary, Glasgow, over the last 9 years and a retrospective survey of the impact of this trend has been carried out.

Patients and methods

All patients admitted as an emergency to the Western Infirmary, Glasgow, with evidence of upper gastrointestinal haemorrhage are initially cared for by the receiving surgical unit but are routinely reviewed by the Haematemesis Management Team (HMT) at 8 a m. on the day following admission. This team, which has functioned since 1977, consists at any one time of a consultant surgeon with an interest in upper GI surgery and a senior medical gastroenterologist Upper GI endoscopy is performed in all patients suspected of having had a gastrointestinal bleed and if this or the patient's history provides evidence of significant upper GI blood loss the HMT assumes responsibility for further care The decision to operate to achieve haemostasis is taken by the HMT surgeon after consultation with his medical colleague and is usually based on clinical and haematological evidence of continuing or recurrent haemorrhage from the lesion seen at endoscopy. The surgical procedure employed is entirely the choice of the operating surgeon and no directives have been laid down. Surgical policy is, however, discussed at HMT meetings and audit can influence group practice

All patients who underwent urgent surgery for bleeding gastric ulceration between 1977 and 1985 at the Western Infirmary, Glasgow, were identified from theatre books and their case records retrieved. The following data were accurately determined from the case notes for each patient: age, sex, dyspeptic history, steroid or non-steroidal anti-inflammatory drug (NSAID) therapy, position of ulcer, pre-operative and total transfusion requirements, type of operation, grade of surgeon, interval from admission to surgery, duration of operation, duration of hospital stay and postoperative outcome. Information on ulcer size was rarely sufficiently well recorded to be of value in comparing groups. Patients who were treated by undersewing alone have been recently traced and if possible interviewed by telephone or postal questionnaire.

Patients who presented with bleeding gastric cancers identified endoscopically were excluded from this analysis. Ulcer biopsy was carried out at operation in all patients not treated by gastrectomy ($n=42$) and no unexpected malignancies were found in this series Over the last 4 years (for patients treated by undersewing alone), it has become our practice to prescribe H_2 receptor antagonist therapy in full dose postoperatively. This is continued for at least 6 weeks and thereafter the reviewing clinician dictates the pattern of prescribing.

Results

In the nine-year period from 1977 to 1985 inclusive, a total of 61 patients underwent urgent surgery for bleeding gastric ulceration at the Western Infirmary, Glasgow. This represents a

Table 1 *Operations performed 1977–1985*

	Partial gastrectomy	Undersewing + vagotomy and drainage	Undersewing alone
1977–81	15	12	6
1982–85	4	10	14

Table 2 *Mortality*

	Number	Hospital deaths	(Mortality)
Partial gastrectomy	19	5	(26%)
Undersewing + vagotomy and drainage	22	10	(45%)
Undersewing alone	20	2	(10%)

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Table 3 *Comparison of patient groups*

	PG	U+V and D	U
Age (mean)	59·8	65·3	64·8
Sex M:F	10:9	6:16	7:13
Patients receiving NSAID	2	7	2
Dyspeptic history <1 month	11	12	9
Transfusion (units) (mean)			
Pre-op.	6·6	5·6	6·5
Total	10·9	9·2	8·2
Delay before surgery (days) (mean)	2·4	3·1	2·4
Surgeon			
Consultant	9	16	11
Senior registrar	10	6	9
Operating time (min) (mean)	127	100	72
Hospital stay (days) (mean)	29·4	19·1	18·6

PG, partial gastrectomy; U+V and D, undersewing+vagotomy and drainage; U, undersewing alone

16 per cent incidence of surgery for bleeding gastric ulceration over the time period studied. Of the 61 patients in this review 19 had a partial gastrectomy, 22 had undersewing of the ulcer plus a truncal vagotomy and drainage, and 20 had undersewing alone. The trend away from radical to more conservative procedures is convincingly demonstrated by the figures in *Table 1* and reflects a rationalization of the requirements for urgent surgery for bleeding gastric ulceration.

Mortality rates for the three types of operation are shown in *Table 2*. The difference in mortality between the vagotomy group (45 per cent) and the undersewing alone group (10 per cent) is statistically significant ($P<0{\cdot}01$). No explanation for these differences in mortality could be found by analysing factors such as age, sex, severity of bleed, delay before surgery and grade of surgeon (*Table 3*) Three consultant surgeons performed 60 per cent of the operations and each carried out all three types of procedure at various times. The trend away from resective surgery was associated with shorter operating times and in-patient hospital stay (*Table 3*).

Of the total deaths (17), 5 were due to surgical causes; anastomotic breakdown in 2 patients and continued or recurrent haemorrhage in 3. The remaining 12 deaths were due to 'medical' causes, the commonest being respiratory failure, occurring in 6 patients, and myocardial infarction in another 3. Neither of the deaths in the undersewing alone group was due to a surgical cause. In the 20 patients in this series who were treated by undersewing alone postoperative rebleeding occurred only once and was satisfactorily managed by transfusion alone.

Follow-up data

Follow-up of the 18 patients discharged from hospital after undersewing of a bleeding gastric ulcer revealed that 3 had died within a year of discharge from unrelated causes, 2 had developed further gastric ulceration induced by non-steroidal anti-inflammatory drug therapy in 1 and alcohol abuse in the other. Two patients could not be traced but the remaining eleven (73 per cent of current survivors) are well with no significant upper gastrointestinal symptoms after a mean follow-up period of 37 months.

Discussion

Until recently simple undersewing of a bleeding gastric ulcer was reserved for patients who were gravely ill and considered unfit for more extensive procedures. As a consequence of this the reported results of undersewing alone are extremely poor[10] and a recent surgical textbook condemned undersewing as an inadequate treatment which frequently led to recurrent haemorrhage[11]. The results presented here suggest that simple undersewing of a gastric ulcer which has bled produces results which are certainly no worse than more conventional surgical therapy and that rebleeding is not a problem (1 of 20 in this series) if the ulcer is adequately undersewn. Our practice is to undersew any identifiable bleeding points with fine suture material and when haemostasis is achieved to obliterate the ulcer cavity with heavier material in an effort to control the feeding vessels beneath and at the margins of the ulcer. The operation rate of 16 per cent in bleeding gastric ulceration reported here is low by comparison with other published series[10,12,13] and this small proportion of patients coming to surgery would be expected to contain those likely to have a high mortality and morbidity. This may in part explain the high mortality in the vagotomy group. Furthermore since the undersewing alone group were unselected their mortality of 10 per cent appears particularly low.

It is now usual that patients who present with a bleeding gastric ulcer are elderly[2,11,14]. In this study the mean age of the patients was 65·7 years with 60 per cent of patients over 60 years of age. Patients in this age group have a high incidence of associated medical conditions and this is reflected in the fact that the majority of perioperative deaths in this series were due to cardiovascular, respiratory and cerebrovascular causes. This agrees with observations made by Vellacott *et al.* who reported that almost two-thirds of deaths after surgery for bleeding gastric ulceration were due to cardiorespiratory causes[2]. In view of this, any attempt to minimize surgical trauma which is consistent with a satisfactory outcome would appear to be well founded. We believe that the perioperative and short-term follow-up results in these patients confirm our suggestion that simple undersewing plus biopsy should be considered as an effective surgical treatment for patients requiring intervention for haemorrhage from a gastric ulcer.

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Splenectomy and renal allograft survival in the rat

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The effect of splenectomy on renal allograft survival is not clear. In the rat, spleens isolated from recipients with functioning grafts have been shown to be a major source of cells that are capable of suppressing the rejection response (suppressor T lymphocytes). Thus the removal of the spleen in these allograft recipients could be detrimental to renal allograft survival. This study investigates this hypothesis, and looks for the presence of suppressor cells in other lymphoid organs apart from the spleen. In the rat renal allograft model, donor Lewis spleen cells given to DA recipients intravenously 1 week before transplantation of a Lewis kidney leads to indefinite allograft survival (median survival time (MST) > 100 days). Splenectomy before or after pretreatment with donor spleen cells failed to abrogate this effect (MST > 100 days). Experiments were performed in which cells or serum were prepared from long-term surviving splenectomized animals which had already been pretreated and transplanted, and then were injected into untreated recipients (adoptive transfer experiments). This was done to determine if cells capable of suppressing graft rejection were present in lymphoid organs outside the spleen in these splenectomized recipients. Thus the IV transfer of 10^8 lymph node cells harvested from splenectomized DA recipients with a long-term surviving LEW graft (LTS), into untreated but lightly irradiated (200 rad) DA recipients resulted in indefinite survival of a fresh Lewis kidney (MST > 100 days). In contrast, adoptive transfer of normal DA lymph node cells was ineffective (MST 13 days). Thus splenectomy is not necessarily detrimental to graft survival, as cells capable of preventing graft rejection are found in other lymphoid organs, such as lymph nodes, in splenectomized recipients.

Keywords: Splenectomy, antigen-induced suppression, renal transplantation

The precise role of the spleen in the immune response to a renal allograft is not clear. Since Starzl introduced the practice of splenectomy before renal transplantation in 1963[1] there have been a series of papers both advocating[2–7] and refuting[8–11] the benefit of splenectomy. Stuart *et al.*[6] carried out a prospective randomized trial of splenectomy in renal transplantation, and found that it increased the survival of both the grafts and the recipients, some of the patients being followed for up to 4 years. Fryd *et al.*, also in a prospective randomized trial, showed increased graft survival for up to 2 years post-transplant[7]. However, Alexander[12], in an analysis of the long-term effects of splenectomy, found that the operation improved renal allograft survival for the first 2 years but thereafter any benefit was lost as there was an increasing death rate from infection in the splenectomized recipient, 50 per cent of deaths in this group being due to infection, compared with 27 per cent in the unsplenectomized group.

In experimental models there is similar confusion as to the exact role of the spleen in the maintenance of allograft survival. Kountz and Cohn[13] found that splenectomy had no effect on the survival of renal transplants in mongrel dogs, although re-analysis of their data by Fabre and Batchelor showed that splenectomy had resulted in a slight but significant increase in graft survival[14]. Several groups have found splenectomy in the rat[14–19] to improve, to varying degrees, the survival of heart or renal allografts; in contrast, other studies have shown that splenectomy had an adverse effect on the survival of renal allografts in the rat[20] and of allogeneic heart transplants in mice[21].

Two hypotheses have been put forward to explain the effect of splenectomy. On the one hand, it has been suggested that lymphocytes reactive against the foreign antigens of the allograft (which may be responsible for rejection) are trapped by the spleen; thus splenectomy after transplantation may lead to prolonged allograft survival by removing a large percentage of antigen-reactive cells. By contrast, it has also been demonstrated that the spleen is a major site for suppressor T lymphocytes that are responsible for the prevention or suppression of allograft rejection[22]; removal of these cells by splenectomy could lead to allograft rejection. These two hypotheses may not be mutually exclusive, as both types of cell may be in the spleen together. If the predominant cell type changes with time, splenectomy at different times in relation to pretreatment and transplantation may have different effects. Indeed, the resultant effect of splenectomy on allograft survival would seem to be multifactorial depending on, among other things, the animal model used[23], the timing of splenectomy in relation to transplantation[14,18] and the timing of splenectomy in relation to other forms of antigen- or antibody-induced suppression[18].

In the LEW ($RT1^l$) to DA ($RT1^a$) donor recipient strain combination, we have previously shown that indefinite renal allograft survival (median survival time (MST) > 100 days) can be achieved by pretreating recipient animals intravenously with 10^7 viable spleen lymphocytes 7 days before transplantation[24,25]. Pretreatment with third-party WAG ($RT1^u$) spleen cells was ineffective (MST 10 days). The aim of the current study was to investigate the role of the spleen in the induction and maintenance of specific unresponsiveness by donor leucocytes. (Specific unresponsiveness means that the recipient animal is unable to mount an immune response against donor histocompatibility antigens as expressed on the renal allograft,

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but is able to mount a normal response against an allograft from any other strain of rat or, indeed, any other antigenic challenge.) In order to test the hypothesis that the spleen has a unique role in the maintenance of allograft survival, we sought to abolish the beneficial effect of specific immunosuppression created by donor spleen cells, by splenectomy at various times both before or after pretreatment, as well as before and after transplantation. We also investigated whether cells capable of suppressing graft rejection were present in lymphoid organs outside the spleen.

Materials and methods

Animals

Male rats of the Lewis–RT1^1 (LEW), blood group D Agouti–RT1^a (DA), Wistar Albino Glaxo–RT1^u (WAG) and (LEW × DA)F$_1$ strains, bred in the John Radcliffe animal house, were used in all experiments.

Pretreatment, transplantation and splenectomy

Recipients were injected intravenously (IV) with 10^7 donor (LEW) or third-party (WAG) spleen cells 7 days before renal transplantation. Orthotopic transplantation of LEW kidneys into DA recipients with delayed nephrectomy was performed essentially as described before[26]. Splenectomy was carried out through an upper midline incision under ether anaesthesia; the splenic vessels were ligated carefully with silk, avoiding damage to the pancreas.

Splenectomy of the recipient was performed at different times in relation to pretreatment with 10^7 donor spleen cells. Thus, in the first group of experiments, splenectomy was carried out 24 h before pretreatment with donor spleen cells (8 days before transplantation, Group 1). In the second group of experiments, splenectomy was carried out at various times between pretreatment of the recipient and transplantation, at 1 h, 3 h, 1 day and 4 days after pretreatment (Groups 2–5). In the third group of experiments splenectomy was performed at the time of transplantation (Group 6), and finally, in the fourth group splenectomy was performed 1 day after transplantation (Group 7).

Preparation of spleen cells

Spleen leucocytes were prepared by passing the spleen through a sieve into phosphate buffered saline. After removing larger particles, the supernatant was centrifuged at 1000 rev/min for 10 min. Contaminating erythrocytes were removed by lysis in Trizma® ammonium chloride buffer for 5 min. The cells were washed three times, resuspended in normal saline, and checked for viability by staining with fluorescein diacetate and ethidium bromide.

Adoptive transfer experiments

Lymph node cells (10^8) from long-term surviving DA recipient animals were prepared in a similar fashion to the spleen cells and adoptively transferred, IV, to untreated recipients of the same strain (syngeneic) 1 day before transplantation of a fresh LEW kidney. The fresh DA recipients had been lightly irradiated (200 rad) 2 days before transplantation but were otherwise untreated[23] (*Figure 1*)

Adoptive transfer of serum was performed by giving 2 ml serum from a DA recipient long-term surviving LEW kidney, IV, at the time of transplantation of a fresh (LEW × DA)F$_1$ kidney into an untreated recipient.

Results

Pretreatment with donor spleen leucocytes (Table 1)

DA rats pretreated 7 days before transplantation with a single IV dose of 10^7 donor (LEW) spleen cells accepted a LEW graft indefinitely (Group 8). The effect was donor specific as pretreatment with 10^7 WAG cells had no effect on graft survival, all kidneys being rejected within 10 days (Group 13).

Splenectomy and renal allograft survival (Table 1)

At no stage did splenectomy abolish the long-term graft survival produced by pretreatment with 10^7 donor spleen cells (Groups 1–7). However, it does appear that splenectomy has some positive effects for, while untreated non-splenectomized animals rejected their grafts in 10 days (Group 9), splenectomy in untreated DA recipients 6 days before a LEW kidney also delayed the course of rejection (MST 16 days, Group 10) and two of the five animals in this group accepted their kidney grafts indefinitely with normal blood urea levels at 100 days (67 mg/100 ml and 75 mg/100 ml, respectively). Furthermore, in the third-party control group, splenectomy of a DA recipient 24 h after pretreatment with 10^7 WAG spleen cells also delayed the onset of rejection (MST 16 days, Group 12). In contrast, splenectomy alone 1 day after transplantation in untreated DA

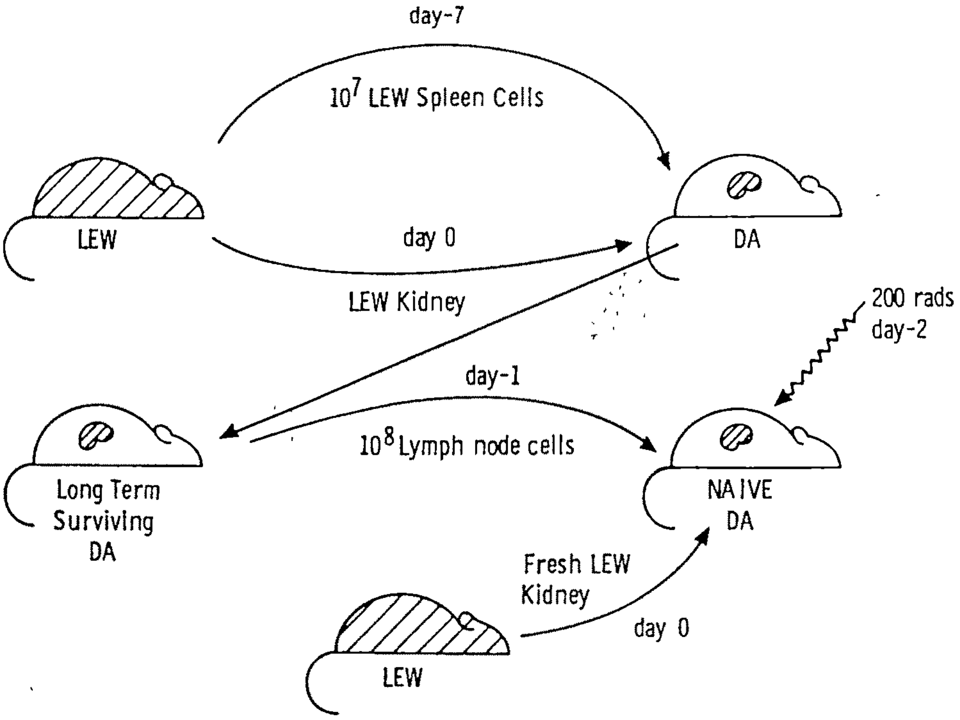

Figure 1 *Adoptive transfer experiments. Lymph node (or spleen) cells (10^8) from long-term surviving (LTS) DA animals were transferred into lightly irradiated (200 rad) naive (i.e. untreated) DA recipients, 1 day before transplantation of a fresh LEW kidney. LEW, donor rats of the Lewis-RT1^l type; DA, recipient rats of the blood group D Agouti-RT1^a type; NAIVE DA, fresh DA recipients*

Table 1 *The survival of LEW renal allografts in DA recipients following pretreatment with LEW or WAG spleen cells and splenectomy before or after pretreatment*

Group	Strain of donor cells	Timing of splenectomy: In relation to pretreatment	Timing of splenectomy: In relation to transplantation	Number of animals	Survival (days)	MST* (days)	*P* value†	Mean blood urea day 10 (mg/100 ml)
1	LEW	−24 h	−8 days	5	18, >100 (×4)	>100	<0·05	167
2	LEW	+ 1 h	−7 days	5	8*, 10, >100, (×3)	>100	n.s.	185
3	LEW	+ 3 h	−7 days	5	10*, 10, >100, (×3)	>100	n.s	176
4	LEW	+24 h	−6 days	5	70, >100, (×4)	>100	<0·05	132
5	LEW	+ 4 days	−3 days	5	67*, >100, (×4)	>100	<0·05	164
6	LEW	+ 7 days	0	5	10, >100, (×4)	>100	<0·05	185
7	LEW	+ 8 days	+1 day	5	>100 (×5)	>100	<0·05	210
8	LEW	—	—	8	70*, >100 (×7)	>100	<0·01	133
9	—	—	—	6	5*, 10 (×4), 11	10	n.s	401
10	—	—	−6 days	5	10, 11, 16, >100 (×2)	16	n.s	235
11	—	—	+1 day	5	10 (×4), 11	10	n.s	375
12	WAG	+24 h	−6 days	5	12, 15, 16, 18, 45	16	<0·05	287
13	WAG	—	—	5	10 (×3), 11 (×2)	10	—	437

MST, median survival time; LEW, Lewis–$\mathrm{RT1}^{l}$ rats; DA, blood group D Agouti $\mathrm{RT1}^{a}$ rats, WAG, Wistar Albino Glaxo–$\mathrm{RT1}^{u}$.
P values were obtained using the Mann–Whitney *U* test, comparing the group of animals pre-treated with donor spleen cells with those treated with third-party controls. * Not rejected

Table 2 *Adoptive transfer of cells into naive irradiated DA recipients before they received a fresh LEW kidney*

Donor to recipient	Cells transferred	Number of animals	Survival	MST (days)	Mean blood urea day 10 (mg/100 ml)
LEW to DA	LTS DA (spleen)	5	>100 (×5)	>100	215
	LTS DA (lymph node)	6	10, 14, >100 (×4)	>100	234
	Normal DA (spleen)	5	13 (×2), 14 (×3)	14	345
	Normal DA (lymph node)	4	13 (×2), 14, >100	13	305
WAG to DA	LTS DA (spleen)	5	12, 13 (×3), 14	13	300
	LTS DA (lymph node)	3	13 (×2), 14	13	354

LTS, long-term survivor, LEW, Lewis-$\mathrm{RT1}^{l}$ rats; DA, blood group D Agouti $\mathrm{RT1}^{a}$ rats; and WAG, Wistar Albino Glaxo-$\mathrm{RT1}^{u}$ rats.
10^8 cells were transferred, intravenously, 1 day before transplantation of a fresh LEW kidney into naive DA recipients pre-irradiated with 200 rad 2 days before transplantation

Table 3 *Passive enhancement of* $(\mathrm{DA}\times\mathrm{LEW})\mathrm{F}_1$ *to DA kidney allografts by serum from splenectomized DA rats bearing long-term surviving LEW kidney allografts*

Serum	Dose of serum (ml)	Number of animals	Survival	MST (days)	Blood urea day 10 (mg/100 ml)
Nil	0	3	10, 10, 11	10	460
Hyper immune DA anti-LEW	1	3	>100 (×3)	>100	185
From long-term survivors	2	3	11, 12, 13	12	386

Recipient animals were pre-treated intravenously with 1 or 2 ml serum at the time of transplantation. MST, median survival time, DA, blood group D Agouti $\mathrm{RT1}^{a}$ rats; LEW, Lewis $\mathrm{RT1}^{l}$ rats

recipients failed to influence the rejection of the LEW kidney (Group 11).

Adoptive transfer of cells or serum from recipients with long-term surviving kidney grafts

Adoptive transfer of 10^8 spleen cells from long-term survivors into untreated DA recipients which were subsequently challenged with a fresh DA kidney graft showed suppressor activity (*Table 2*). Furthermore, adoptive transfer of 10^8 lymph node cells from splenectomized DA recipients with a long-term surviving renal allograft into untreated DA recipients, which were subsequently challenged with a fresh LEW graft (*Figure 1*), also resulted in prolonged survival of the LEW graft, four out of six animals going on to long-term survival with normal blood urea levels (*Table 2*). In contrast, the majority of control animals that received lymph node cells from untreated DA animals died at 13 days, although one animal did go on to long-term survival with normal blood urea levels after an initial rise at 10 days (*Table 2*).

Survival of $(\mathrm{DA}\times\mathrm{LEW})\mathrm{F}_1$ to DA allografts was not influenced by the administration of serum from long-term surviving kidneys (MST 12 days). This is in contrast to treatment of DA rats with hyperimmune DA anti-LEW serum (passive enhancement) which results in long-term renal allograft survival (MST >100 days) (*Table 3*).

Discussion

The spleen has been shown to be an important site of proliferation and maturation of immunocompetent cells reactive against an allograft[14]. A number of previous studies, therefore, have examined the removal of these immunocompetent cells by splenectomy in an attempt to prolong allograft survival. Fabre and Batchelor showed that splenectomy, in the absence of any other treatment, up to 7 weeks before transplantation prolonged allograft survival in the rat, and was associated with a decreased lymphocytotoxic antibody response to the graft[14]. Silber *et al.*[17] also found a prolongation of allograft survival in their splenectomized control groups, where $1{\cdot}5\times10^8$ spleen cells syngeneic with the recipient were given 24 h before transplantation. The latter study was based on the concept that antigen-sensitive lymphocytes might be recruited to the spleen of the recipient after pretreatment with donor spleen cells, and then these cells would be removed from the recipient by splenectomy, thus causing deletion of the alloreactive cells and allowing prolonged survival of a subsequent graft.

In this study we have shown that splenectomy before grafting in untreated recipients and in recipients pretreated with third-party cells 7 days before grafting resulted in some prolongation of graft survival. Indeed, two out of five untreated animals splenectomized 6 days before grafting accepted their LEW kidneys indefinitely (*Table 1*, Group 10, 12) This confirms earlier work and supports the hypothesis that splenectomy may remove a population of immunocompetent cells which potentially can respond to the allograft, although obviously the effect of splenectomy is modest in this strain combination. Perhaps surprisingly, no beneficial effect was seen when splenectomy was carried out 1 day after the transplant (*Table 1*, Group 11) suggesting that already at this stage the cells reactive against the graft are more widespread in their distribution and are present outside the spleen in greater numbers than before transplantation.

Although the spleen has been shown to be a source of immunocompetent cells reactive against an allograft, it is also known that the spleen is a major source of suppressor cells in several rodent models[27–31] including rats bearing long-term surviving allografts[31]. This study confirms these findings. Suppressor cells have not been demonstrated in the rat after pretreatment with blood alone, and a secondary stimulation provided by a graft would appear to be required to produce them[22]. However, in mice, Shelby and co-workers have demonstrated the presence of suppressor cells in the spleen after transfusion alone[32]. On this basis, our experiments were designed to abolish the effect of donor pretreatment with spleen lymphocytes, on the assumption (for which we have some evidence; I. V. Hutchinson, unpublished observations), that suppressor cells are important in the inductive phase of suppression, and the spleen is a major source of these cells. That splenectomy did not abolish the effect of pretreatment with donor spleen cells suggests that the spleen is not the only site where suppressor cells become activated. This hypothesis was tested by setting up the adoptive transfer experiments using lymph nodes (*Figure 1*). The results demonstrate that suppressor activity was present in the cells prepared from the lymph nodes of splenectomized animals bearing long-term surviving allografts (*Table 2*). These cells were capable of prolonging survival when transferred to naive DA recipients, 1 day before transplant of a fresh LEW kidney. In contrast, no effect was seen after adoptive transfer of serum from splenectomized animals (*Table 3*). Thus, it would appear that suppressor activity resides in the cellular rather than the humoral component, as demonstrated by these adoptive transfer experiments[22].

Earlier work carried out by Banowsky and co-workers[18] demonstrated that splenectomy followed by three donor-specific blood transfusions produced enhanced allograft survival. The authors suggested that the prolonged graft survival observed was due to the generation of suppressor cells in sites other than the spleen, especially the lymph nodes. Although suppressor cells were harder to induce in sites outside the spleen, it was possible to do so by giving several transfusions, one transfusion alone being ineffective. When recipient animals were transfused before splenectomy, graft survival was not prolonged, suggesting that suppressor cells were present primarily in the spleen after transfusion, and that splenectomy removed this population of suppressor cells which were of critical importance for maintaining graft survival. These results were not supported by Martin and co-workers[33], they were unable to abrogate the donor-specific transfusion effect by splenectomy at the time of transplantation.

In our experiments we were unable to abrogate the beneficial effect of pretreatment with spleen leucocytes by splenectomy at any stage before or after transplantation. However, we were using donor spleen lymphocytes to produce specific unresponsiveness in contrast to whole blood, and it is possible that spleen lymphocytes are a more potent stimulator of suppressor cells than whole blood. Certainly, it would appear that if suppressor cells are responsible for preventing graft rejection in this model, then they can be induced in sites other than the spleen, such as the lymph nodes.

It would seem likely that splenectomy alone before transplantation removes a major, but not the only, site for recognition and entrapment of foreign antigen and the proliferation of antigen-sensitive cells[14]. After antigen pretreatment, the spleen appears to be a major source of suppressor cells which may have a role in the inductive, as well as the maintenance, phase of enhancement[21]. Thus survival or destruction of the allograft will depend, among other things, on the relative proportions of these activated lymphocyte populations and this could explain why different results have been reported from different laboratories. The effects of splenectomy on graft survival in pretreated and untreated animals will depend on the timing of splenectomy in relation to transplantation, and the distribution of the differing lymphocyte subpopulations in the recipient at the time of splenectomy, which may be related to the experimental model used

Acknowledgements

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Growth rate of human tumour xenografts measured in nude mice by in vivo cast modelling

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Caliper measurement of xenograft tumour volume incurs shape-dependent errors of up to 230 per cent. A more sensitive and accurate method is described for repeated in vivo *measurement of tumour volume by cast modelling. The technique can provide electronic data for further analysis and its accuracy and limitations can themselves be determined. Week-on-week changes in tumour volume may be detected with up to 99 per cent confidence.*

Keywords: Xenograft, nude mice, volume measurement

Xenografts of human tumours into athymic nude mice are increasingly used as a tool for clinical research, and tumour volumes are usually measured *in vivo* with skin calipers. This technique introduces a subjective element in terms of the pressure applied and of the determination of maximum and minimum diameters. Furthermore, any approximation formula (*Table 1*)$^{1-3}$ to calculate volume from these two measurements will be appropriate only to tumours of one shape.

I present here an alternative method based on cast modelling and independent of any geometrical approximation. The technique yields reproducible results and is suitable for serial *in vivo* measurements of xenograft tumour volume in nude mice housed in an isolator.

Materials and methods

Tumour casts

Tumours. Tumour implants must be made over an area of the body wall which offers some resistance to pressure, e.g. the ventral chest wall. In addition to facilitating constant moulding pressure, this implantation site appears not to be liable to extensive deep invasion by the implant.

Primary moulds. Impressions in soft alginate gel are taken from the unanaesthetized animal, the most suitable material is 'Alginoplast fast-setting' (Bayer, Newbury, UK), a dental moulding compound which combines easy wetting of the powder with rapid curing. At 24°C a gel is formed in under 2·5 min, with 'snap-setting' during the last 15–20 s. Before gelation, and unlike some other alginate compounds, the mixture is so soft and compliant that is flows easily around the tumour without significant pressure. Aliquots of powder (5·75 g) and water (12·5 ml) are conveniently prepared in disposable containers which may be stored inside a mouse isolator. Water and powder are rapidly stirred together and the paste loaded into a disposable histology casting mould; this process takes 30 s. The quantities given fill a 25 × 35 mm well. For a 25 × 25 mm well, 4 g of powder is appropriate. The mouse is held in a prone position by the nuchal skin and the base of the tail and pressed gently but firmly into the soft paste. The body temperature of the mouse locally accelerates gelation and the mouse needs to be held in place for only 45–60 s, after which the gel separates easily from the animal. Moulds lacking a clear demarcation between tumour and body wall are repeated, but this is rarely necessary. Details of animal identity and experiment can be marked on the side of the plastic tray.

Secondary casts. Alginate gels shrink on drying out and the moulds must be kept under water until a permanent positive cast has been taken. The most suitable material is a dental plaster of Paris, Geostone (Bayer, Newbury, England), curing time may be prolonged by keeping the mix on ice. The mould is mopped dry, and wet plaster laid in a little at a time, with a small spatula, up to the demarcation of the body wall. Hardened casts can be extracted after about 15 min and any swarf scraped off.

Volume determinations

Once the casts have been allowed to dry out thoroughly, tumour volume may be determined by weighing the casts. Volume in microlitres will be the weight in milligrams divided by the density of hardened Geostone. With a suitable balance, the data may be fed directly to a microcomputer for further analysis.

Results

Calibration

Once set Geostone has a density of 2·22 g/cm^3; repeated density determination using disposable ELISA plate wells of volume 270 μl gave a standard error around this mean figure (s.e.m.) of only 0·2 per cent for 16 separate mixes.

Ten replicate casts were made of the same tumour on the same day to determine the scatter for the complete measuring process (*Table 2*). For these replicates the s.e.m ranges from 5 per cent for 50 μl tumours to 2 per cent at a volume of 780 μl. Thus, variations in moulding pressure and animal movement appear not to introduce large errors, probably because the paste is compliant and gels rapidly on contact with the warm mouse.

If Student's *t* test is applied between average measurements of different-sized tumours (here the same tumour at different times, *Figure 1*), it can be seen that the system detects 20 per cent changes in tumour volume at the 99 per cent confidence level for 400 μl tumours and with 98 per cent confidence for 50 μl tumours.

Cast modelling was compared with caliper measurement by applying the usual formulae to caliper diameters of a semi-ovoid cast of known volume. *Table 3* compares the volumes determined.

Measured cast volume was correlated with tumour weight by making replicate measurements of tumours, killing the animals, and excising and weighing the tumours on the same day (*Table 4*). If tissue density is taken as 1, tumour volume is uniformly underestimated by only 12 per cent—tissue does, of course, have a slightly higher density and so the underestimate is really less than this figure.

Table 1 *Formulae for tumour volume approximation*

Formula	Reference
$V = L \times W^2/2$	1
$V = \pi/6 \times L \times W^2$	2
$V = (L \times W)^{3/2}$	3

V, volume; L, length; and W, width

Table 2 *Scatter of replicate volumes determined by cast modelling*

Mean volumes in μl ± s.e.m.						
46 ± 2 (4%)	56 ± 2 (4%)	195 ± 10 (5%)	356 ± 17 (5%)	434 ± 12 (3%)	774 ± 14 (2%)	1408 ± 56 (4%)

This work was previously presented orally at the VIIIth Meeting of the European Association for Cancer Research, Bratislava, 1985

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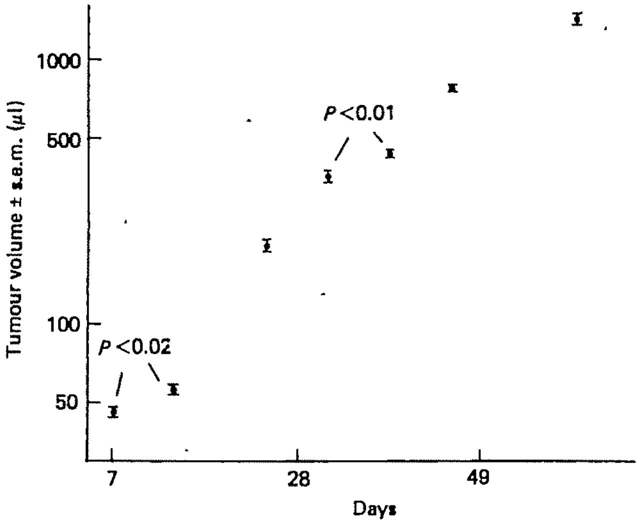

Figure 1 *Typical tumour growth curve, mean tumour volume derived from ten replicate measurements of the same tumour on each day*

Discussion

The formula $V = L \times W^2/2$ (reference 1) commonly employed for approximation of tumour volume, yielded a value which was 225 per cent of the actual volume of a typical specimen cast (*Table 3*), even if allowance was made for caliper pressure on a tumour specimen. This overestimate will depend on the shape of the tumour. An alternative formula, such as $V = \pi/12 \times D^3$ for a hemisphere, would clearly fail for multilobular or elongated tumours.

The cast modelling technique differs from the plethysmographic method of Delorme[4] by being sensitive enough to allow very small tumours to be quantified; also, it is substantially more accurate than the use of calipers. By using a secondary casting technique the problems of surface tension inherent in the liquid method of Vofkori[5] are avoided. Like any measuring system, cast modelling introduces its own error, but that error is itself measurable, calculable and largely independent of tumour shape, unlike that generated with calipers. A 230 per cent overestimate is undesirable in any measurement; the present system on the other hand is adequately accurate to reveal non-Gaussian distribution of tumour size within a group of replicate animals. Such a finding can significantly alter the interpretation of tumour xenograft experiments.

Table 3 *Cast modelling compared with caliper measurement*

Formula	Estimate (µl)	Percentage of true volume
$V = L \times W^2/2$	800	225
$V = \pi/6 \times L \times W^2$	837	250
$V = \pi/12 \times D^3$	575	165
Volume measured	(356)	(100)

V, volume, L, length; W, width; and D, diameter

Table 4 *Cast volumes compared with tumour weight*

	Volume (µl)	s.e.m. (%)	Weight (mg)	Underestimate (%)
T1	198	5	218	12
T2	53	5	62	13

T1 and T2 refer to the replicate tumour measurements

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Improvements in the treatment and prognosis of colorectal carcinoma

In a survey of the surgical results in 709 patients with colorectal carcinoma (CRC) treated between 1976 and 1985 a favourable shift of stage distribution was observed. The tumour was localized (Dukes' classification A or B) in 61 per cent of patients, as compared with 47 per cent in the previous 10-year period. This change was, in part, due to different interpretation of stage definitions. Clear improvements of the results were, however, also noted. Radical surgery was possible in 76 per cent of patients and the primary tumour was removed in 93 per cent. Surgical mortality was 4·4 per cent and complication rate 15 per cent, significantly less than earlier (6·5 and 38 per cent, respectively). Increasing numbers of sphincter-saving operations were performed in rectal cancers (47 per cent as compared with 24 per cent in the previous 10-year period). The overall 5-year survival rate improved from 40·5 to 52·5 per cent. Premalignant conditions were identified in 12·6 per cent of patients: previous CRC 4·8 per cent, cancer family syndrome 4·1 per cent, ulcerative colitis 1·7 per cent and familial adenomatosis 0·6 per cent. In order to sustain the favourable trend of improving survival prospects, more emphasis must be directed to the detection of early stage cancers.

Keywords: Colorectal carcinoma, premalignant conditions, cancer screening

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Colorectal carcinoma (CRC) represents the third most common malignancy in Finland with about 1500 new cases annually, and the incidence has been constantly rising over the last three decades, being 18–21 per 100 000 population per year in 1982[1]. The prognosis of CRC patients is principally determined by the extent of spread of the tumour at the time of diagnosis[2,3]. In 1966–1975 more than half of our patients already had metastases at the time of surgery[4].

During the last 10 years, various developments have taken place in diagnostic techniques for CRC; double-contrast radiology and colonoscopy have become routine examinations. In addition, more formal hemicolectomies have been performed, rather than segmental resections, and rectal preservation has become the rule in tumours of the upper and middle rectum. To study the influence of such changes the surgical results in CRC at our department were surveyed in the last 10-year period, 1976–1985, in comparison with the previous 10-year report from the same department[4]. Special emphasis was placed, in the search, on looking for further areas for improvement, e.g. identifying high risk groups amenable to screening for CRC.

Patients and methods

The records of all patients with CRC treated primarily between January 1976 and December 1985 at the Second Department of Surgery, University Central Hospital in Helsinki, were reviewed by the authors. Altogether 709 patients had invasive adenocarcinomas, 12 of these were included twice because of metachronous CRC within the study period. The distribution of the tumours by location is shown in *Figure 1* (22 synchronous tumours in 19 patients included). There were 334 men and 375 women with a mean age of 64·3 years, ranging from 18 to 91 years.

The extent of spread of the tumours was determined using the clinical and operative records and the histopathological report of the specimen, and each case was classified according to the Turnbull modification of Dukes' classification[5]. However, the definition of Dukes' A to 'D' was that described in the ACPS-system[3]. Tumours which had directly invaded adjacent organ(s), and could be reliably removed, were classified as B and not 'D', which was the classification used if any tumour was left behind Dukes' 'D' was also used in case of distant spread, even when all distant metastases could be removed

The mode of presentation, type of surgery, postoperative complications, mortality (within 30 days or during the same hospital admission) and 5-year survival were determined from the clinical records Inadequate data concerning survival were completed using the official census registry of Finland, and in all cases where the cause of death was unknown the official death certificates were obtained from the Central Statistical Office of Finland Cancer specific 5-year survivals by

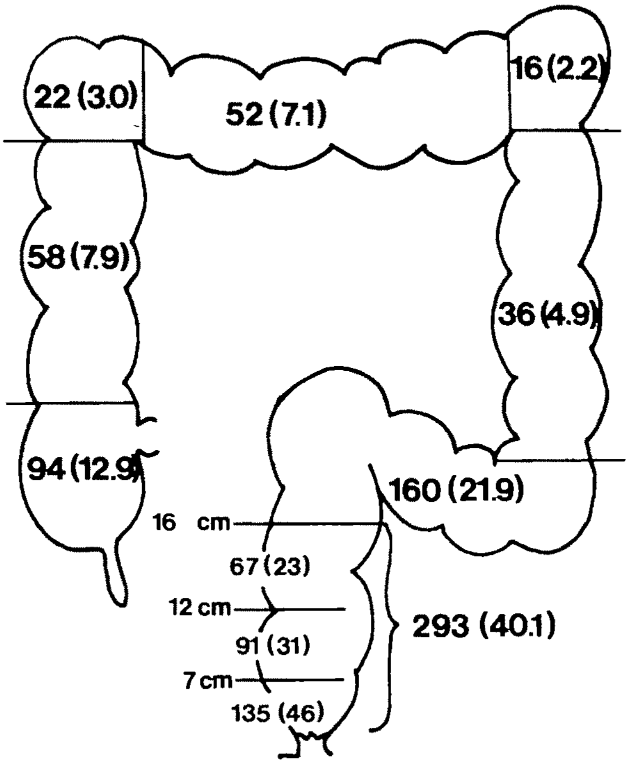

Figure 1 *Site distribution of 731 colorectal carcinomas in 709 patients, percentages in parentheses (distribution within rectal tumours shown separately)*

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Table 1 *Classification of tumours in colorectal carcinoma patients within two 10-year periods*

Modified Dukes' classification	Number of patients 1966–1975	Number of patients 1976–1985
A	166 (25·3)	142 (20·0)
B	146 (22·2)	293 (41·3)*
C	87 (13·2)	92 (13·0)
'D'	258 (39·3)	182 (25·7)
Total	657 (100·0)	709 (100·0)

* Adjacent organ invasion suspected in 49 Dukes' B cases (6·9 per cent of all): histologically proven in 8, histology negative in 7, and histology inconclusive or not available in 34 cases. Numbers in parentheses are percentages

Table 2 *Relation between mode of presentation and tumour classification*

	Tumour classification				
Presentation	A	B	C	'D'	All
Asymptomatic	12	5	4	—	21 (3·0)
Symptoms					
Elective operation	128	258	77	152	615 (87·4)
Emergency operation	2	30	11	25	68 (9·7)

Numbers in parentheses are percentages. Five patients not operated on are excluded

stage were calculated using the actuarial life table method of Greenwood; no age correction was applied.

In the search for specific predisposing conditions for CRC, definite cases of previous CRC or colorectal adenomas, verified ulcerative colitis or familial adenomatosis were approved criteria. For cases of cancer family syndrome (CFS) at least two other first degree relatives with CRC were required; any less definite family history was recorded as suggestive of CFS.

Results

Tumour stage

The CRCs of the present 10-year period were diagnosed at a more favourable stage than those during the previous one: 61·3 per cent of patients had a localized tumour as compared with 47·5 per cent before, and the proportion of Dukes' 'D' tumours decreased from 39·3 to 25·7 per cent (*Table 1*). Most patients continued to be diagnosed on the basis of typical symptoms (97·0 per cent), but the number of patients requiring emergency surgery decreased from 15·5 to 9·7 per cent. *Table 2* shows the advantage of less extensive spread of tumours when detected in an asymptomatic phase as compared with cases found in symptomatic and complicated phases.

Results of surgery

Altogether 538 patients (75·9 per cent) underwent 'curative' surgery, including 11 patients with histopathologically verified distant metastases (Dukes' 'D'). A further 122 patients had palliative resection of the primary tumour giving rise to an overall resectability rate of 93·1 per cent. Thirty-four patients had various bypass procedures or diverting colostomy, five patients had palliative local treatment such as cryocoagulation, and ten had laparotomy with biopsy.

A total of 31 patients died postoperatively (4·4 per cent), 23 (3·6 per cent) after elective and 8 (11·8 per cent) after emergency operations. Three deaths were related to surgical complications all requiring re-operation, one of these because of anastomotic dehiscence. All the other 28 deaths were due to general complications.

The overall rate of postoperative complications (excluding urinary infections) was 108 (15·3 per cent) and of those requiring re-operation 40 (5·7 per cent). Anastomotic breakdown occurred in thirteen cases, seven (6·8 per cent) after anterior rectal resections and six (1·5 per cent) after other resections. Four of the leaking low anastomoses were stapled and three were hand-sewn, two of the latter after using abdomino-transsacral approach. In one of these cases the rectum had to be excised later and in another the diverting colostomy was permanent. After abdominoperineal rectal excision, perineal wound infection was the most common complication observed in 29 patients (24·4 per cent). Other major complications included abdominal wound infection (19), wound rupture (7), bowel obstruction (9), thrombo-embolic complications (10), intra-abdominal haemorrhage (6) and ureteric lesion (3).

Anal sphincter preservation was possible in 133 patients (46·5 per cent) with rectal tumours and in 92, 63 and 19 per cent of cases with tumours of the upper-, middle- and lower-third of the rectum, respectively.

Survival

The cancer specific uncorrected 5-year survival by the extent of tumour spread is shown in *Figure 2*. The overall survival was 52·5 per cent, clearly exceeding the figure of 40·5 per cent for the previous 10-year period. Even though this effect was mostly due to the more favourable distribution of tumour classification, slight improvements were observed within Dukes' A (91·5 *versus* 80·7 per cent) and B (69·0 *versus* 61·6 per cent), while the survival figures for C and 'D' remained unchanged. Two patients with proven distant metastases (ovary, liver) survived for over 10 years after they had both had, apparently, radical surgery and no other treatment.

Predisposing conditions

Undisputable precancerous conditions, which form a clear or potential indication for a systematic screening programme if identified in good time, were observed in 89 (12·6 per cent) of patients (*Table 3*). Additionally, 13 of the women (3·5 per cent) previously had endometrical cancer and 14 (3·7 per cent) breast cancer; these high frequencies might signify an aetiological association with CRC. Previous cholecystectomies, on the other hand, were not observed at a greater frequency than expected: 62 cases (8·7 per cent) were recorded.

Discussion

The prognostic trend in CRC in our department, since systematic studies were started in the 1950s, has been favourable. The crude 5-year survival between 1950 and 1962 was 29–37 per cent (colon cancer)[6], between 1966 and 1975 it

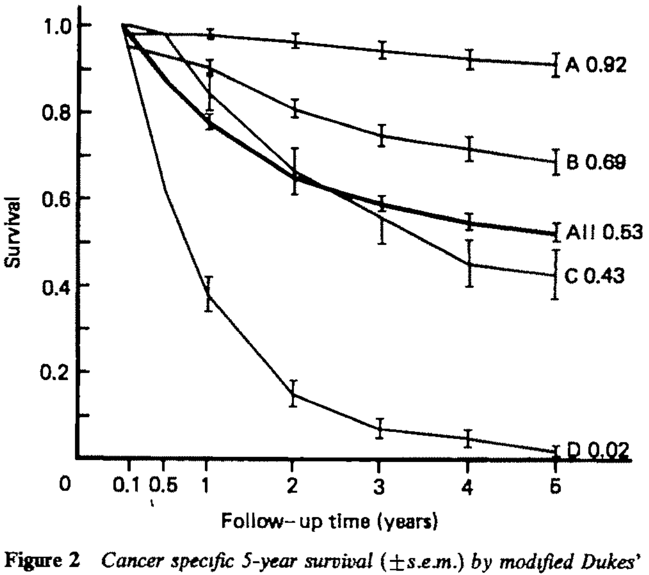

Figure 2 *Cancer specific 5-year survival (±s.e.m.) by modified Dukes' classification*

Table 3 *Premalignant conditions by Dukes' classification in 709 colorectal carcinoma (CRC) patients*

Condition	Tumour class A	B	C	'D'	Total
Previous CRC	10	13	4	7	34 (4·8)
Previous colorectal adenoma	8	4	2	3	17 (2·4)
Cancer family syndrome (CFS)	7	6	3	—	16 (2·3)
Suspected CFS	3	7	—	3	13 (1·8)
Ulcerative colitis	1	3	1	7	12 (1·7)
Familial adenomatosis	3	1	—	—	4 (0·6)
Juvenile polyposis	—	1	—	—	1 (0·1)
Ureterosigmoidostomy	—	—	—	1	1 (0·1)
Total*	28	32	9	20	89 (12·6)

* In some cases several premalignant conditions co-existed, which explains the unequal total and sum figures

was 40·5 per cent[4], and now 52·5 per cent. At the same time, operative mortality has fallen from 7 to 13 per cent in the 1950s to 6·5 per cent in the next 10-year period and yet further to the present 4·4 per cent. The lower mortality can be attributed to improved anaesthesia, postoperative fluid therapy and nutrition, and to prophylactic measures against thrombotic and septic complications. Nevertheless, all these advances may still have less influence on survival than does the shift towards earlier tumour stages.

Another clear trend is the increased rate of sphincter preservation in rectal cancer beginning in the late 1970s and still rising, with the advent of stapling devices since 1980. The number of anterior rectal resections nearly doubled with few technical failures and without any increase in complications. On the contrary, the complication rate was higher after abdominoperineal excision than after anterior resection due to frequent perineal wound infections (24 per cent). In fact, a sphincter-saving rate of up to 75 per cent can be achieved nowadays[7,8] if the distal margin of clearance is reduced to 2·0 cm, which is regarded as permissible[9,10].

Our increasing survival figures are in contrast to reports from many centres with stabilized survival prospects for long periods[11–13]. The essential change in our series was the reducing rate of Dukes' 'D' tumours and of those requiring emergency surgery. The great difference between the two periods, however, reflects, in part, the use of the ACPS-system in the latter period instead of the Turnbull system used before. In the present series, 49 cases with Dukes' B tumours (6·9 per cent of all) were under suspicion of adjacent organ invasion. True invasion was histologically proven in a minority of such cases; this has been considered necessary for classifying as 'D' in the Turnbull system[12]. In our view, it is more logical to reserve 'D' only for cases which are partially irremovable and for those with distant metastases, as defined in the ACPS[2,3], even though a small proportion of tumours with distant metastases are amenable to radical surgery.

The fact that the proportion of Dukes' A lesions diminished, instead of increasing in the present series, might signify a more accurate classification due to improved histopathological documentation This is also the most probable explanation for the higher survival figures for Dukes' A and B.

In order to detect more Dukes' A cancers, increasing emphasis must be placed on screening examinations of asymptomatic patient groups, who are at high risk for CRC[14]. A hint of the advantage of screening was seen in the very favourable stage distribution of the 3·0 per cent of patients detected by screening in this series. It was also demonstrated that more high risk patients were available for screening if the underlying conditions had been recognized. The number of patients with metachronous cancer was surprisingly high, 4·8 per cent. It was observed that the greatest failures due to defective surveillance programmes occurred in patients with ulcerative colitis and in those with previous CRC or adenomas, i.e. 24 cases with metastatic tumour in these groups.

Another interesting risk group suitable for screening studies is formed by the autosomal dominant inherited CRC syndromes, familial adenomatosis and cancer family syndrome. While familial adenomatosis is well recognized as a high risk condition and largely in control, the greater number of cancer family syndrome patients are an increasing challenge because of problems in their identification and in the more demanding screening methods needed[15]. The number of cancer family patients in the present series (4·1 per cent) is probably still an underestimate as accurate family histories were not obtained in all cases; the true frequency of cancer family cases seems to be more than 5 per cent of all CRCs in Finland[16]. In the whole series a precancerous condition was identified at quite a high frequency, 12·6 per cent, as has been observed in some previous reports[17,18]. Because most of these conditions concern especially young and middle-aged adults, their impact on the overall survival in CRC must not be regarded as small.

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Prognostic significance of DNA ploidy in colorectal cancer: a prospective flow cytometric study

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A prospective study of prognostic factors has been carried out in a group of 123 consecutive patients with colorectal cancer. The fate of all patients is known at 3 years after operation. Clinical and pathological data were recorded at the time of presentation and operation, and the patients have been subject to regular postoperative review. DNA ploidy status was determined by flow cytometry. In all, 39 (33 per cent) patients had DNA diploid tumours and 80 (67 per cent) patients had DNA aneuploid tumours. In four cases, tumour material was not obtained. The patients with DNA aneuploid tumours had a worse prognosis than those with DNA diploid tumours, but this was only seen in those patients classified as Dukes' B. In a Cox's regression analysis, the surgeon's assessment of operability was the strongest predictor of survival, followed by the pathological classification and the patient's age. After these factors had been considered, the DNA ploidy status conferred no independent survival value.

Keywords: Colorectal cancer, DNA, ploidy, flow cytometry

Colorectal cancer is a major cause of mortality, accounting for 17 357 deaths in England and Wales in 1985[1]. The overall relative 5-year survival rates range from 19 to 62·3 per cent according to age, sex and tumour site[2].

Clinical and pathological features have been identified which help to predict prognosis and may assist in the selection of patients for adjuvant therapy.

A 'curative' resection, defined as removal of all macroscopic tumour, is associated with a significant survival advantage[3]. Yet, some patients having a 'curative' resection die from their cancer owing to the progression of clinically inapparent disease.

The pathological assessment of large bowel cancer has remained essentially unchanged for 50 years and is based on Dukes' classification[4] and the determination of histological differentiation pioneered by Broders[5]. Modifications to the Dukes' system have been developed to refine its prognostic power, particularly with respect to depth of penetration and location and number of involved lymph nodes[6–8]. Alternative methods of classification have also been developed[9,10], but Dukes' system remains the most widely used. Although Dukes' classification is strongly related to prognosis, anomalies are observed: approximately one-third of patients with Dukes' C tumours become long-term survivors, yet about one-third of patients with Dukes' B tumours die from their cancer. These anomalies may, in part, be due to the subjective nature of pathological assessment. The detection of lymph node metastases is largely dependent on how avidly they are sought, and the assessment of histological differentiation may vary between observers. Consequently, there is a demand for more objective parameters with which to refine the clinical and pathological classification of colorectal cancer.

The measurement of cellular DNA content by flow cytometry is emerging as a prognostic aid in a variety of human tumours[11–13]. Changes in cellular DNA content reflect changes in chromosome content, and tumours can be divided into two groups; those with a normal or near normal diploid DNA content and those with an abnormal, aneuploid, DNA content. The DNA diploid group includes tumours with minor chromosomal re-arrangements because changes involving a few chromosomes are not distinguished.

In colorectal cancer, though a survival advantage has been suggested for patients with DNA diploid tumours, compared with those with DNA aneuploid tumours, there is a lack of unanimity regarding the prognostic significance of ploidy status. Differing DNA aneuploidy rates and clinical and pathological correlations have been reported[14–25] (*Table 1*), and a precise role for ploidy determination in the clinical setting has yet to emerge. In order to clarify the significance of DNA ploidy, a group of patients with colorectal cancer has been prospectively studied. DNA ploidy status has been determined using a standardized technique[26] applicable to routinely processed clinical specimens.

Patients and methods

Patients

The study group consisted of 123 consecutive patients presenting from 1981 to 1983 with colorectal cancer. Extensive clinical and pathological details were collected at the time of presentation and stored at the University of Manchester Regional Computing Centre. All have been followed prospectively, by out-patient review or research nurse, and the outcome is known for all patients at 3 years.

The operating surgeon reported a 'curative' resection if all macroscopic tumour was removed. If there was residual local disease or clinically apparent hepatic metastases, surgery was deemed 'non-curative'. Histological differentiation and Dukes' classification were determined on routinely processed specimens. Tumour tissue was not obtained from 4 patients with clinically advanced disease, therefore, 119 were assessable by flow cytometry.

Flow cytometry

Samples for flow cytometry were prepared using the method of Hedley *et al.*[26], using all available paraffin-embedded tumour blocks. The presence of representative tumour tissue was confirmed on a 4 µm haematoxylin and eosin section. Adjacent 30 µm sections were cut, dewaxed in two changes of xylene (each for 10 min), rehydrated through decreasing concentrations of ethanol (100, 95, 70, 50 per cent, each for 10 min) and washed twice in distilled water. Nuclei were released by cytoplasmic digestion, using 0·5 per cent pepsin in 0·9 per cent NaCl (pH 1·5) for 30 min at 37°C. Release of nuclei was enhanced by intermittent vortex mixing. Samples were centrifuged, and washed nuclear pellets were resuspended in 1 µg of 4',6-diamidino-2-phenylindoldihydrochloride (DAPI) per millilitre of RPMI tissue culture medium. DAPI is a fluorescent dye that binds to DNA. The quantity of DAPI bound is directly proportional to DNA content.

Stained nuclear suspensions were filtered through 35 µm nylon mesh and analysed on a FACS IV cell sorter (Becton Dickinson, Sunnyvale, California, USA), using ultra-violet excitation and blue fluorescent emission collected via a 408 nm-long pass filter. Fluorescence intensity is

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Table 1 *DNA aneuploid rates and prognostic significance of DNA ploidy in colorectal cancer*

Reference	n	Aneuploid (%)	Follow-up (years)	Survival (%)		P
				Diploid	Aneuploid	
Fresh						
Quirke[14]	50	72	–	–	–	–
Rognum[15]	85	67	–	–	–	–
Banner[16]	56	71	–	–	–	–
Hiddeman[17]	88	82	–	–	–	–
Frankfurt[18]	91	68	–	–	–	–
Wolley[19]	33	39	5	65	8	–
Melamed[20]	33	55	3	53	67	n.s.
Rognum[21]	100	63	5	59	43	n.s
Paraffin-embedded						
Armitage[22]	134	54	5	43	19	0·005
Kokal[23]	77	65	5–8	100	62	<0·001
Goh[24]	203	64	15	67	46	0·007
Quirke[25]	125	54	5	57	35	<0·02

–, Data not included, n.s., not significant

directly proportional to the quantity of nuclear bound DAPI, and therefore directly proportional to its DNA content. A total of 20 000 nuclei in each sample were analysed and DNA histograms constructed. Normal colonic mucosa was used to calibrate the flow cytometer at the start and during the course of a run.

Coefficient of variance for the diploid peak was calculated using the incorporated software If a coefficient of variance > 10 was obtained the analysis of the sample was repeated but considered valid if still > 10.

Tumour samples invariably contain normal diploid stromal cells, hence all DNA histograms contain a diploid peak which serves as an internal control. Any other G_0/G_1 peak comprising at least 10 per cent of the total histogram was considered to represent an aneuploid population.

The DNA content of aneuploid nuclei was estimated by calculating the DNA index (DI), i.e. the ratio of the fluorescence intensity of the aneuploid population compared with the diploid population. Differences of DI greater than 0·2 in different blocks from the same tumour were considered to represent different DNA stem lines.

Statistics

Correlations between DNA ploidy and clinical and pathological features were examined using the χ^2 test. Survival curves were constructed using the life table method and analysed using the Statistical Package for the Social Sciences[27]. The independent significance of prognostic variables was determined by Cox's multivariate regression analysis (BMDP2L program, University of California, Los Angeles, USA).

Results

Interpretable DNA histograms were obtained for all tumours examined by flow cytometry, with a mean coefficient of variance of 7·1 (range, 3·8–12·5). In all, 39 (33 per cent) were DNA diploid and 80 (67 per cent) DNA aneuploid. Examples of DNA histograms are shown in *Figure 1*.

A mean of three (range, one to six) blocks were analysed for each tumour. In seven cases, one block only was analysed and six of these were DNA aneuploid. The DNA ploidy status (diploid or aneuploid) was usually, but not invariably, identical in different blocks taken from the same tumour. Analysis of one block only would have resulted in 'correct' DNA ploidy determination in at least 75 per cent of cases, and analysis of two blocks in at least 90 per cent of cases.

Distribution according to DI is shown in *Figure 2*. Seven DNA aneuploid tumours with a DI of 1·1–1·9 had a discernible proliferating aneuploid S and G_2 population (*Figure 1*). Twenty tumours had a DI between 1·9 and 2·1 ('tetraploid') but only one of these had a discernible S and G_2. Multiple DNA stem lines were detected in only three cases.

Involved lymph nodes from 41 of the Dukes' C tumours were examined by flow cytometry. A total of 23 were of identical DNA ploidy status to the primary (7 DNA diploid and 16 DNA aneuploid); in 18 the primary tumour was DNA aneuploid, but an aneuploid population was not detected in the lymph node metastases. Of the 16 DNA aneuploid lymph node metastases, 15 had an identical DI to the primary tumour.

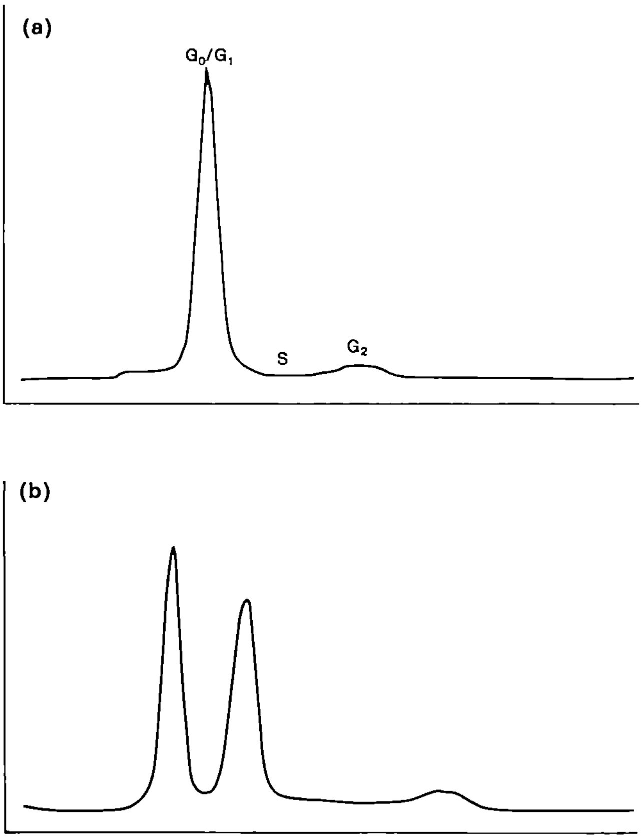

Figure 1 *DNA histograms,* y *axis, number of nuclei;* x *axis, fluorescence intensity (DNA content);* **a**, *DNA diploid (G_0, G_1, S, and G_2 represent resting and proliferating cells in different phases of cell cycle),* **b**, *DNA aneuploid*

Age

The mean age was 68·7 years (range, 39–93 years) and a significantly higher proportion of DNA aneuploidy occurred in the more elderly (*Table 2*).

Tumour site

There was no significant difference in DNA aneuploidy when left sided and right sided tumours were compared.

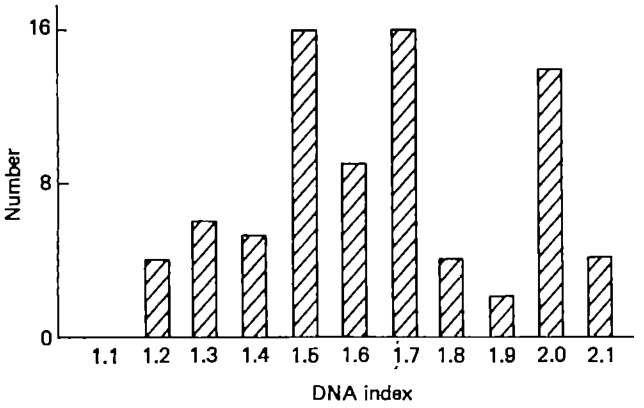

Figure 2 *Distribution of aneuploid tumours according to DNA index* (n=*80*)

Table 2 *Age and DNA ploidy in 119 patients with colorectal cancer*

	n	<70 years	>70 years
Diploid	39	23	16
Aneuploid	80	29	51
Total	119	52	67

χ^2=4·62, 1 d.f., $P<0{\cdot}05$

Table 3 *'Curative' resection and DNA ploidy in 119 patients with colorectal cancer*

	n	'Curative'	'Non-curative'
Diploid	39	33	6
Aneuploid	80	52	28
Total	119	85	34

χ^2=4·03, 1 d.f., $P<0{\cdot}05$

Table 4 *Dukes' classification and DNA ploidy in 114 patients with colorectal cancer*

	n	A	B	C
Diploid	39	4	26	9
Aneuploid	75	6	33	36
Total	114	10	59	45

χ^2=6·73, 2 d.f., $P<0{\cdot}05$

'Curative' resection

There was a significantly higher proportion of DNA aneuploid tumours in patients in whom a 'curative' resection was not achieved, compared with those having a 'curative' resection (*Table 3*).

Histological differentiation

The incidence of DNA aneuploidy tended to increase with decreasing histological differentiation. In all, 25 out of 40 (63 per cent) of well differentiated, 41 out of 60 (68 per cent) moderately differentiated and 13 out of 18 (72 per cent) poorly differentiated tumours were DNA aneuploid. However, these differences were not significant (χ^2=0·64, 2 d.f., P=n.s.).

Dukes' classification

DNA aneuploid rates for Dukes' A and B tumours were similar, but the rate for Dukes' C tumours was significantly greater (*Table 4*).

Survival

DNA ploidy status was significantly related to prognosis; 64 per cent of patients with DNA diploid tumours, but only 34 per cent of those with DNA aneuploid tumours, survived 3 years (χ^2=7·25, 1 d.f., P=0·007) (*Figure 3*).

There was a possible survival advantage for patients with DNA diploid tumours within the sub-group having a 'curative' resection, but this did not reach statistical significance: 24 out of 33 (73 per cent) with DNA diploid tumours survived compared with 26 out of 52 (50 per cent) with DNA aneuploid tumours (χ^2=3·36, 1 d.f., P=0·07).

Only one of ten patients with a Dukes' A tumour died, and this death was not cancer related.

There was a significant independent survival advantage for patients with DNA diploid tumours within Dukes' B; 73 per cent of patients with DNA diploid tumours survived 3 years compared with 45 per cent of those with DNA aneuploid tumours (P=0·035, *Figure 4*).

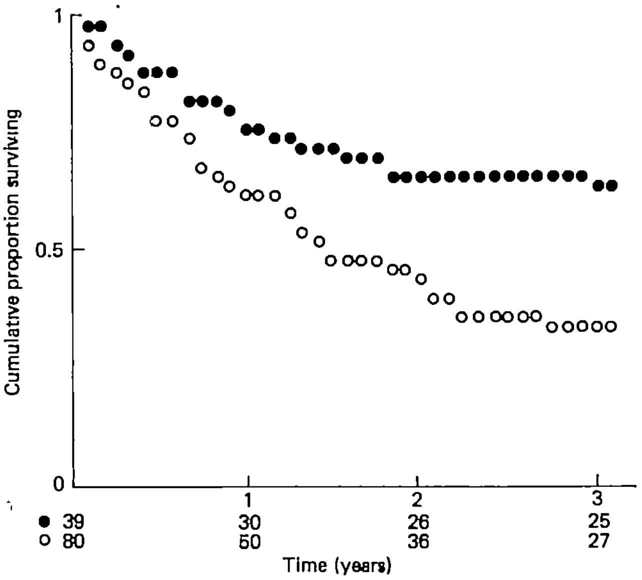

Figure 3 *Comparison of 3-year survival for patients with DNA diploid* (●) *and aneuploid* (○) *tumours.* χ^2=*7·27, 1 d.f.,* P=*0·007. Subscripted numbers represent survivors*

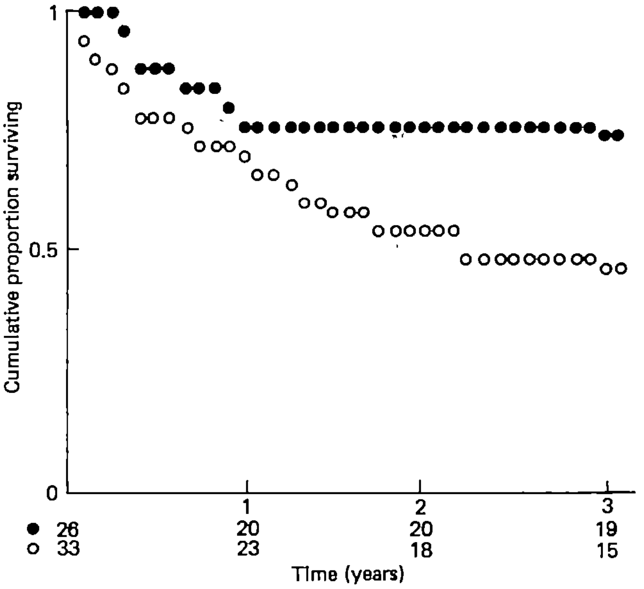

Figure 4 *Three-year survival for patients with Dukes' B tumours; DNA diploid* (●) *compared with DNA aneuploid* (○). χ^2=*4·47, 1 d.f.,* P=*0·035. Subscripted numbers represent survivors*

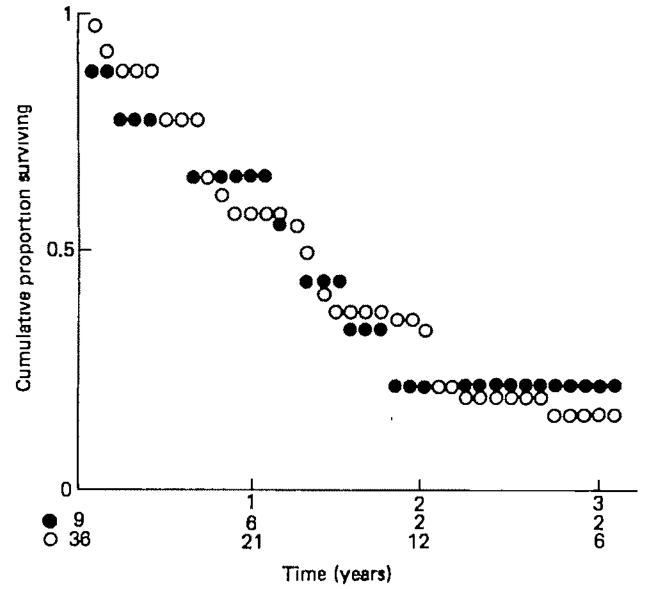

Figure 5 *Three-year survival for patients with Dukes' C tumours. DNA diploid (●) compared with DNA aneuploid (○).* $\chi^2 = 0{\cdot}04$, *1 d.f.,* P=0·8. *Subscripted numbers represent survivors*

For patients with Dukes' C tumours the prognosis was poor regardless of ploidy status (*Figure 5*).

Survival rates were compared for aneuploid subgroups according to DI: 20 out of 60 patients (33 per cent) with a DI of 1·1–1·8 survived 3 years compared with 7 out of 20 (35 per cent) of those with a DI of 1·9–2·1.

Variables of individual prognostic significance were: 'curative' resection ($\chi^2 = 27{\cdot}72$, 1 d.f., $P < 0{\cdot}001$), Dukes' classification ($\chi^2 = 17{\cdot}05$, 2 d.f., $P < 0{\cdot}001$), histological differentiation ($\chi^2 = 12{\cdot}23$, 2 d.f., $P = 0{\cdot}002$) and DNA ploidy status ($\chi^2 = 7{\cdot}27$, 1 d.f., $P = 0{\cdot}007$). In a Cox's multivariate regression analysis model, the most powerful prognostic indicator was the surgeon's clinical assessment of achievement of a 'curative' resection; the only other two variables of independent significance were Dukes' classification and the patient's age. Similarly, if the regression analysis was limited to patients having a 'curative' resection, DNA ploidy status did not confer independent prognostic significance.

Discussion

Chromosomal re-arrangements are a recognized feature of many human tumours including colorectal cancer[28,29]. Cytogenetic studies have shown that the majority of large bowel tumours have an abnormal aneuploid karyotype, usually with an increase in chromosome number and the appearance of structurally abnormal 'marker' chromosomes[30,31]. Gross chromosomal changes are reported to be associated with an aggressive clinical course in colorectal cancer[32].

Cytogenetic karyotyping has been relatively successful in the haematological malignancies and characteristic abnormalities have been discovered, such as the Philadelphia chromosome of chronic myeloid leukaemia and the 8:14 translocation of Burkitt's lymphoma which involves the c-*myc* oncogene. These techniques have been less successful in solid tumours because the metaphase spreads necessary for karyotyping are more difficult to obtain.

Quantitative changes in chromosome complement can be estimated indirectly by measuring cellular DNA content by static or flow cytometry. In colorectal cancer static studies suggested a worse prognosis for patients with DNA aneuploid tumours[33] but the laborious nature of the technique has precluded widespread clinical application. The ability to measure cellular DNA content has been greatly facilitated by flow cytometry—techniques and technology are now sufficiently refined to be of clinical utility.

Using flow cytometry, Wolley *et al.*[19] reported that 65 per cent of patients with DNA diploid tumours survived 5 years compared with only 7·5 per cent of those with DNA aneuploid tumours. This engendered optimism that the objective determination of DNA ploidy status by flow cytometry would be superior to existing subjective clinical and pathological classification in determining the prognosis for patients with colorectal cancer. Subsequently, a lack of unanimity has arisen about the prognostic value of DNA ploidy status (*Table 1*). Kokal *et al.*[23] found DNA ploidy status to be the single most important prognostic factor in a group of patients having a 'curative' resection. Armitage *et al.*[22] and Quirke *et al.*[25] report DNA ploidy status to be of individual and independent significance in a multivariate analysis, but weaker than Dukes' classification. Goh *et al.*[24] found that although DNA ploidy was of individual prognostic significance, it contributed little when included in a regression analysis model. Melamed *et al.*[20] and Rognum *et al.*[21] report no significant differences in survival between patients with DNA diploid and DNA aneuploid tumours.

Conflicting results may be due to selection bias in retrospective studies, relatively small numbers studied, differing techniques, or may reflect misinterpretation of the true biological significance of DNA ploidy status. In the present study, errors have been minimized by prospectively studying all patients presenting during the study period, utilizing a reproducible technique for paraffin-embedded material[26].

The mean coefficient of variance of 7·1 is consistent with other studies using paraffin-embedded material, but higher than for fresh tissue. The proportion of aneuploid tumours and their distribution according to DI is in accordance with studies using either fresh or fixed tissue (*Table 1*), so it appears unlikely that a significant number of aneuploid tumours with a low DI have been missed. If the determination of DNA ploidy status by flow cytometry assumes prognostic value, the use of routinely processed specimens would be practically advantageous.

Sampling is probably as important as methodology in the detection of aneuploidy, and errors have been minimized by examining all representative tumour blocks. If analysis had been limited to only one block the 'correct' ploidy status would have been determined in 75 per cent of cases. Similarly Quirke *et al.*[14] found that analysis of one block alone would result in correct ploidy determination in 72 per cent of cases. Differences between blocks may reflect tumour heterogeneity or sampling error, but it becomes axiomatic that multiple blocks should be analysed to maximize detection of aneuploidy.

The pattern of DNA aneuploidy, according to DI, varied between tumours, but appeared relatively constant within the primary tumour and lymph node metastases.

Multiple DNA stem lines were detected in only three cases in the present study, but have been reported in up to 40 per cent cases in other studies[17]. However, precise criteria for defining multiple stem lines are rarely stated so studies may not be directly comparable. Atkin[30] using cytogenetic techniques found that samples from different areas of a tumour, had identical or sufficiently similar karyotypes, suggestive of single clonal origin. Schwartz *et al.*[34] measured tumour DNA content by flow cytometry in synchronous large bowel carcinomas and found they were often of identical ploidy status and DI. It was suggested, this could represent a common tumour origin, perhaps due to translumenal metastases.

In the present study, DNA aneuploidy was associated with both clinical and pathological features of aggressive malignancy. DNA aneuploid tumours were more likely to be fixed, a 'curative' resection less likely, and lymph node metastases more likely to be present.

The presence of a detectable aneuploid population did not invariably confer an aggressive phenotype, indeed, DNA aneuploidy is a feature of 6–27 per cent of benign colorectal polyps[35–38], and has been detected in chronic ulcerative colitis[39,40] which predisposes to malignancy. Although the generation of an aneuploid population may occur early in the process of malignant transformation, it is not a prerequisite for malignant behaviour because diploid tumours may also exhibit an aggressive phenotype. If chromosomal re-arrangements are necessary for malignant transformation they are presumably sub-chromosomal or limited to a few chromosomes and not detected by these techniques.

DNA ploidy was of individual prognostic significance ($P=0{\cdot}007$) but not of independent significance in a regression analysis model. These findings support the studies of Armitage *et al.*[22], Quirke *et al.*[25] and Goh *et al.*[24], where DNA ploidy was significantly related to survival but weaker than Dukes' classification. In this study, patients with Dukes' A tumours had a good prognosis irrespective of ploidy status and patients with Dukes' C tumours had a poor prognosis whether DNA diploid or aneuploid. However, these data should be interpreted cautiously in view of the small number of Dukes' A and DNA diploid Dukes' C tumours. Finan *et al.*[41] studied patients with hepatic metastases from colorectal cancer and found no significant relationship between DNA ploidy and survival. In the present study, there was, however, a significant independent survival advantage for patients with DNA diploid tumours within the Dukes' B subgroup.

The strongest correlation between ploidy and survival is reported by Kokal *et al.*[23] in a retrospective study of patients having a 'curative' resection. In the present study, although there was a survival advantage for patients with DNA diploid tumours within the subgroup having a 'curative' resection, it did not reach statistical significance.

DNA ploidy determination at biopsy has already been used in an extended system of pre-operative classification of rectal cancer[42]. Since DNA ploidy status alone does not distinguish between a benign polyp and a fixed metastatic tumour, and a diploid biopsy does not confidently exclude aneuploidy, ploidy data must be interpreted cautiously with other clinical and pathological data.

In conclusion, DNA aneuploidy probably represents a cellular epiphenomenon, which is concurrent with malignant progression and is significantly related to prognosis in colorectal cancer. Clinically, the use of routinely processed specimens is justifiable, and the determination of DNA ploidy by flow cytometry complements the existing clinical and pathological classification of colorectal cancer, but at present is unlikely to influence the management of patients.

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Penile incarceration by a metallic object

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Incarceration or strangulation of the penis by an encircling object is an uncommon clinical presentation. This paper describes a simple method to deal with such an emergency in which no special skill is required and no immediate or long-term morbidity related to the treatment occurs.

Case report

A 38-year-old man presented in the casualty department in a distressed and embarrassed state with a large iron nut (outer diameter 3·5 cm, inner diameter 2 cm, width 2 cm), encircling and strangulating the penis at its root. The length of time between the mishap and presentation was approximately 8 h and during this period he had tried several manoeuvres to rid himself of the nut without success. The penis distal to the nut was so swollen that movement of the nut was not only impossible but extremely painful. Although urine had not been passed there was no significant urinary retention. Attempts in the casualty department to remove the nut using lubricants failed because the distal penis was so swollen that the outer surface of the 2 cm deep nut was flush with the penile skin

The patient was taken to the operating room and under light general anaesthesia, a size 19 needle on a 20 ml syringe was inserted into the shaft of the penis on the dorsolateral aspect and suction applied. Dark blood was easily aspirated with local collapse of the swollen penile shaft. Two further punctures were made on either side of the shaft and approximately 25 ml of blood aspirated from each side. This resulted in complete flaccidity of the penile shaft and following the application of liberal amounts of lubricant jelly, the nut was advanced to the corona The glans penis remained swollen and turgid preventing further movement of the nut. Two additional punctures were made in the glans on either side of the midline and a total of 16 ml of blood aspirated. This resulted in flaccidity of the glans and, following further lubrication, the nut was removed without difficulty.

Postoperative analgesia was not required and no difficulty was experienced in micturition. Examination the following day revealed no evidence of trauma apart from the needle puncture marks

Discussion

Penile incarceration with a foreign object is usually associated with an attempt to improve sexual function. Patients usually present at a late stage when the penis is grossly swollen and attempts to remove the object have already failed. Constriction by the encircling object initially causes blockage of the venous return and continued arterial supply results in further swelling of the penis distal to the obstruction. Eventually the arterial supply is also occluded and removal of the constricting agent is a matter of utmost urgency if the penis is to be salvaged. Peters and Sagalowsky[1] recommended sectioning the object with a metal cutting device. In 14 cases described by Dakin[2], 11 were dealt with by sectioning the object, 2 were removed after multiple incisions of the skin and subcutaneous tissues of the penis and in one case, the constricting object was shattered with a hammer blow! Browning and Reed[3] described the use of string to compress the distal penis making it elongated and narrow. Tiwari, Razdan and Yadav[4] reported swelling accompanied by gangrenous patches of the skin such that it was necessary to deglove the distal penis to the level of the cavernous tissue in order to remove a nut. Shellhammer and Donelly[5] have also described a similar case in which removal of the cutaneous and subcutaneous coverings of the penis was necessary before an iron ring could be removed.

Multiple punctures and aspiration of blood from the engorged penis is a simple and safe method which does not require specialized instrumentation. It is suggested that potentially dangerous and mutilating methods of removal of the constricting object should only be used if this treatment fails.

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Complete rectal prolapse: the anatomical and functional results of treatment by an extended abdominal rectopexy

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Between 1970 and 1985 (inclusive), 66 patients presented with complete rectal prolapse; 59 (89 per cent) were treated by extended abdominal rectopexy. Forty-four patients (75 per cent) have been followed for more than 2 years: all cases were cured of their complete prolapse, no patients died, and major complications were few. Constipation (47 per cent) and incontinence (19 per cent) caused serious problems for many patients postoperatively.

Keywords: Rectal prolapse, extended rectopexy, functional results

Complete rectal prolapse is predominantly a disease of old people in the United Kingdom. Many different procedures have been reported but these reports suffer from selection bias for the operation or from incomplete follow-up. In order to avoid these two problems regarding selection and follow-up, in 1970 it was decided to treat all patients presenting with complete rectal prolapse by the same operation ('extended abdominal rectopexy') and to follow the patients indefinitely: feebleness, old age or chronic ill-health would not be accepted as contra-indications to the operation unless it would be inappropriate on clinical grounds to proceed. The operation technique was designed to correct as many of the anatomical defects as possible, and was developed from procedures introduced by Butler[1] and Wells[2].

Although the series was designed to answer the primary problems of the safety and effectiveness of the operative design, the open-ended follow-up enabled the functional results to be assessed.

Patients and methods

Between 1970 and 1985, 66 patients with complete rectal prolapse were seen at either The London Hospital or St. Mark's Hospital Seven patients were excluded from the operation, leaving fifty-nine (89 per cent) who were treated by extended abdominal rectopexy. The average age was 65 years (range 20–86 years), and most patients were female (54 women:5 men).

All patients were asked to attend follow-up indefinitely, and were classified as defaulters if they failed to come for 2 years or more after the operation (unless they were operated on later than 1983). Fifty-one patients (86 per cent) have been followed up with forty-four (75 per cent) being followed for more than 2 years Mean time of follow-up was 58 months (range 2–167 months)

Exclusions (Table 1)

Two young men (aged 22 and 28 years respectively) were not operated on by extended abdominal rectopexy because it was considered that the endopelvic dissection might lead to sexual impotence. both were handled by an intersphincteric postanal repair, and this was successful in one: the failure was later treated successfully by extended abdominal rectopexy with no sexual after-effects. The five remaining patients had varied reasons for exclusion, but only one was rejected because of physical ill-health (case 5). One patient had no ivalon (Prosthex, Prosthex Ltd, UK) inserted because the small intestine was perforated early in the operation when extensive adhesions were being divided from a previous operation (case 4)

Defaulters

Eight patients (14 per cent) were lost to follow-up: three elderly women died from cardiovascular causes within 2 years of the procedure; one patient was permanently confined to a mental institution 3 months after the operation; two other patients refused to attend the clinic after their first and second postoperative visits respectively and the remaining two moved from the district leaving no forwarding address. All patients who defaulted were seen at least once postoperatively and the prolapse was controlled in every case.

Table 1 *Details of seven excluded patients*

Case no.	Sex	Age (years)	Reason for exclusion	Procedure performed	Result
1	M	22	Fear of impotence	Postanal repair	Failure
2	M	28	Fear of impotence	Postanal repair	Success
3	F	65	Minimal prolapse	Postanal repair	Success
4	F	67	Operative contamination	Abdominal rectopexy (no ivalon)	Success
5	F	73	Cardiac 'cripple'	Postanal repair	Success
6	F	75	Senile dementia	Thiersch procedure	Success[*]
7	F	78	Psychosis	Thiersch procedure	Success[†]

[*] Prolapse controlled but patient incontinent
[†] Prolapse controlled but episodes of faecal impaction

Bowel function and continence status were recorded in all patients pre- and postoperatively

The results were collected by the second author (C.H.), who was not involved with the procedure.

Pre-operative assessment (Tables 2, 3 *and* 4)

In addition to the health problems common to a predominantly elderly patient group, many of the subjects suffered specific defects that could promote the development of rectal prolapse or diminish the chance of a successful surgical cure. Many patients also had abnormal bowel habits before the surgical rectopexy, as shown in *Table 3*; constipation was the commonest complaint. (For the purposes of this article a normal bowel habit was defined as 'the passing of a formed stool without excessive straining up to three times per 24 h'. Constipation was defined as 'the need for regular use of medicines to achieve defaecation'.) Many patients also suffered from incontinence (*Table 4*) before surgery.

Operative technique of extended abdominal rectopexy

The operation was designed to correct the anatomical defects present in a patient with a complete rectal prolapse. The important steps are illustrated in *Figures 1–3*, of which the most significant are complete mobilization of the rectum from every aspect (including removal of the peritoneum lining the deep rectovaginal pouch); shortening and re-

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Table 2 *Antecedent factors*

Factor	No.	No. of patients
1. Gynaecological operations		
Hysterectomy	11	11
Abdominal repair of procidentia	2	2
Colporrhaphy	2	2
2. Pelvic floor surgery		
Abdominal rectopexy (no ivalon)	3	3
Postanal repair	1	1
3. Anorectal surgery		
Thiersch procedure	11	6
Submucosal sclerosing injections	5	3
Mucosal excision	3	3
Haemorrhoidectomy	2	2
Anal dilation	1	1
4. Colonic operation		
Total colectomy (for constipation)	1	1
5. Psychotic disorder		
Schizophrenia	2	2
Depression	2	2
6. Spinal operation		
Laminectomy ($L_{3,4}$)	1	1
Spinal fusion	1	
7. Peripheral neuropathy		
Poliomyelitis	1	1
Diabetic neuropathy (severe)	1	1
8. Central neurological disease		
Disseminated sclerosis	1	1
Huntington's chorea	1	1
Acromegaly	1	1

Table 3 *Bowel function before and after operation*

Pre-operative		Postoperative	
Abnormal (86%)		Abnormal (83%)	
Constipation	17		28
Partial incontinence	14		7
Complete incontinence	12		4
Stool frequency (>3 per 24 h)	11		1
Straining defaecation	7		
Irregular bowel habit	2		2
Urgent defaecation	1		
Normal (14%)	8	Normal (17%)	10

Table 4 *Incontinence before and after operation*

Type	Pre-operative	Postoperative
Total	26 (44%)	11 (18·6%)
Faecal	21 (36%)	
Complete	12	2
Soiling	9	9
Mucus	2	0
Flatus	3	0

attachment of the lateral ligaments of the rectum; repair of the rectovaginal septum; and a uterine ventrosuspension procedure. From the procedure's inception, polyvinyl alcohol (ivalon) sponge was used to stiffen the walls of the rectum and was attached to the rectum rather than being stitched down to the presacral fascia, as in the Wells procedure.

The operation should:

1. Elevate, straighten and refasten the prolapsed rectum in the pelvis;
2. Prevent intussusception of the rectal wall;
3. Promote adhesions between the back of the rectum and the front of the sacrum;
4. Tether the upper and middle parts of the rectum to the front of the sacral promontory;
5. Remove the excessively deep anterior peritoneal pouch;
6. Strengthen the rectovaginal septum and obliterate the deep rectovaginal peritoneal pouch;
7. Ventrosuspend the uterus and elevate with it the anterior rectal wall;
8. Restore the peritoneal floor at the level of the pelvic brim.

Thus it corrects virtually every pelvic and rectal defect that is present with two exceptions:

1. The 'gap' in the levator ani muscle is not narrowed;
2. The patulous atonic anus is not strengthened.

In women who have had a hysterectomy, the ventrosuspension procedure is omitted but all the other steps are completed, including both removal of the peritoneal pouch anterior to the rectum and reinforcement of the rectovaginal septum. In men, after removal of the anterior peritoneal pouch, the gap between the top of the prostate and the front of the rectum is closed with interrupted fine unabsorbable sutures before closing the peritoneal floor.

Although in some early cases simultaneous procedures were carried out to strengthen and support the patulous anus (usually by a Thiersch

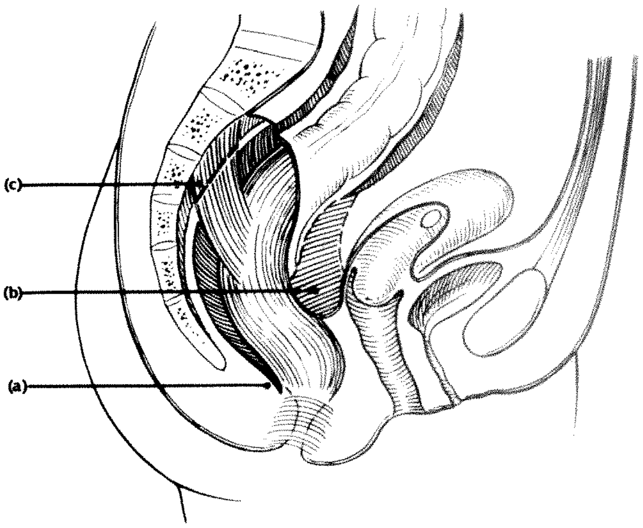

Figure 1 *After dividing the peritoneum of the pelvic floor the rectum is mobilized and straightened. Posteriorly the dissection extends beyond the coccyx (a). Anteriorly the deep extension of the recto-uterine pouch is stripped of its peritoneal covering (b). Laterally, the lateral ligaments of the rectum are freed and divided (c) preparatory to re-fastening to the sacral promontory*

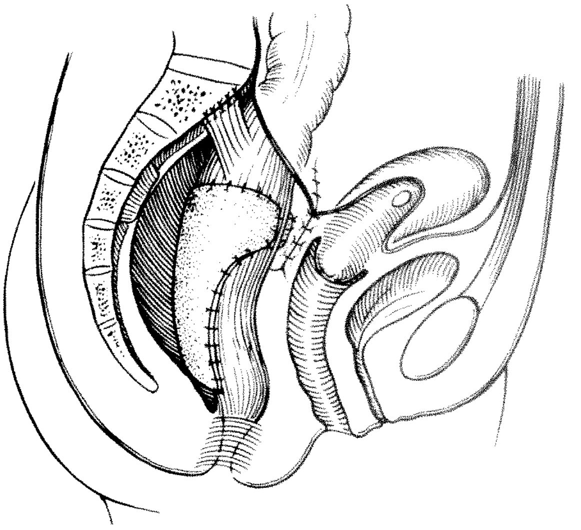

Figure 2 *The prosthesis (ivalon, polyvinyl sponge) is attached to the rectum, with collars at the upper end. No stitches are put into the presacral fascia. The rectovaginal septum is repaired anteriorly and buttressed with stitches (or another piece of sponge). The shortened lateral ligaments are re-attached to the sacral promontory*

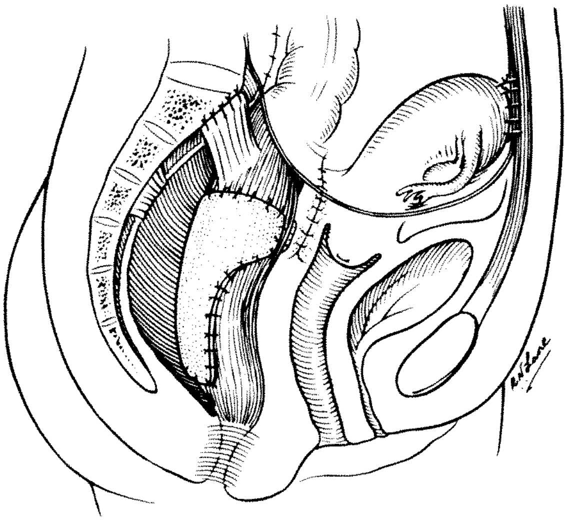

Figure 3 *The sigmoid mesentery and the peritoneum of the pelvic floor are closed; this reconstitution of the pelvic floor should take place at the level of the pelvic inlet. The uterus is drawn upwards and forwards, and attached to the back of the rectus sheath by strong nylon sutures*

procedure), this practice was discontinued early in the series because of poor results (see Results).

Postoperatively, great efforts are made to promote a regular non-straining habit of defaecation. In many cases the patients have continued to need medication with salts, glycerine suppositories or enemas: hydrophylic colloids, such as Normacol (Norgine Ltd, UK), Isogel (Allen and Hanburys Ltd, UK) and mucilage, have usually not been sufficient.

Additional procedures

In two patients additional abdominal procedures were performed: in one patient with severe diverticular changes in the sigmoid colon a left hemicolectomy was performed; the other underwent cholecystectomy for symptomatic gallstones. No complications were associated with these additional intra-operative procedures.

Eight patients underwent immediate additional anal or perianal procedures for a gaping atonic anal sphincter. In seven patients a Thiersch circumferential ligature of silver wire or monofilament nylon was used; in one patient a simultaneous postanal intersphincteric repair was carried out.

Complications (Table 5)

Mortality. All patients survived the operation and left the hospital ambulant and in good condition.

Morbidity in hospital. Twenty-three (39 per cent) patients had complications. The largest group ($n = 16$) was that with retention of urine requiring catheterization on one or more occasions; all regained spontaneous micturition before leaving hospital. The operation involved a mean hospital stay of 19·6 days (range 10–56 days). The longest postoperative stays were in four patients who had, respectively, deep vein thrombosis (32 days), suspected myocardial infarct (36 days), prolonged ileus (38 days) and postoperative morbid depression (56 days).

Morbidity after discharge from hospital. Two patients were re-admitted for adhesion obstruction and were successfully treated operatively. Three patients required 'in-hospital' treatment for (1) faecal impaction, (2) disabling constipation and (3) rectal stenosis: all were managed conservatively. One patient developed a large incisional hernia. In one further patient the sponge was extruded spontaneously through the posterior rectal wall 6 weeks after leaving hospital: this patient complained of 'smelly' stools but was otherwise unaffected by this development for which she was never readmitted: her prolapse had not recurred after a 4-year follow-up.

Results

Specific to the rectal prolapse

The corrective effect of the operation was excellent: all patients were cured of their complete prolapse. Six patients were left with mucosal prolapse, which subsequently required treatment in one patient.

Patulous anal sphincter

In four of the seven patients who received a simultaneous Thiersch procedure, serious problems of painful faecal retention developed, and the wire (nylon) needed to be removed. The result of a postanal repair was satisfactory in the only patient in whom it was used.

Constipation (Table 3)

The number of patients with constipation nearly doubled postoperatively (from 17 (29 per cent) to 28 (47 per cent) patients). For some patients in addition to the routine use of stimulatory drugs, regular home calls by the district nurse to give enemas were required. One patient was readmitted for manual evacuation of faeces under a general anaesthetic; another was admitted for bowel retraining with drugs and diet for intractable constipation; a third patient was readmitted for observation for rectal stenosis associated with constipation, for which no operative treatment was necessary.

Incontinence (Table 4)

Of 26 patients with pre-operative incontinence, 10 were cured of faecal incontinence. A further nine patients still suffered some degree of faecal leakage, for which they wore a protective pad: one of these (who also had a patulous sphincter with mucosal prolapse) was treated successfully 2 years after the extended rectopexy by a Thiersch operation. Two patients remained totally incontinent of faeces postoperatively and required further operative intervention: one patient was treated 6 years after extended rectopexy by a rectal excision with permanent end colostomy; the other was handled by a postanal repair 8 years postoperatively with a good result.

Discussion

The results of this series have confirmed two important points: (1) that an abdominal rectopexy can achieve a successful anatomical result in all cases of complete prolapse of the rectum, provided that a good technique is used; (2) that there are very few patients who must be refused an abdominal repair on grounds of age or infirmity.

Since Goligher stated in 1975[3] that the 'operative treatment of complete rectal prolapse is difficult and frequently unsuccessful' several authors have reported excellent results from abdominal rectopexy procedures[4–9]. In some of these, it has not been divulged how the patients were selected for (and which were refused) the operation, and in others the follow-up criteria were not strict. In this series a deliberate attempt was made to avoid selection bias by subjecting all cases of complete prolapse to the same procedure, and the follow-up was indefinite. The design of the operation was based on the simple hypothesis that the results would be improved by surgical

Table 5 *Complications*

Type	Complication	Number	Percentage
Immediate	Postoperative death	0	0
In hospital	Urinary retention	16	39
(23)	Cardiac arrhythmia	3	
	Cerebrovascular accident	1	
	Prolonged ileus	1	
	Iliofemoral thrombosis	1	
	Depression	1	
Late	Adhesion–obstruction	2	12
(7)	Faecal impaction	1	
	Intractable constipation	1	
	Rectal stenosis	1	
	Incisional hernia	1	
	Prosthesis rejected	1	

correction of all the major anatomical defects, rather than a few, and was an extension of previous techniques designed by Butler[1] and Wells[2]. All our cases were cured by the operation with a follow-up that was almost complete (86 per cent). As the operation of extended abdominal rectopexy is more extensive than other types of abdominal repairs (e.g. the Ripstein operation[8]), the absence of deaths in this series confirms the safety of abdominal rectopexy, even in an elderly population group: our oldest patient was 86 years of age.

Because an extensive pelvic dissection can cause impotence, extended abdominal rectopexy has not been used by us for young men: the two young men with complete prolapse were treated by a postanal repair[10]; the Wyatt procedure[11] could also be used in such cases.

Attempts to improve incontinence associated with a patulous anal sphincter by a Thiersch procedure or its modifications[12] performed at the time of the abdominal rectopexy were extremely disappointing. Many patients suffered extreme difficulty with defaecation, and some became impacted: most complained of severe anorectal discomfort which, in a few, amounted to definite pain. In four of the seven patients who had a synchronous Thiersch procedure, the wire (or nylon) had to be removed. In the one case handled by a simultaneous postanal repair the result was good. In our view, faecal incontinence problems should be handled preferentially by a postanal repair[10] which is best deferred to a second-stage intervention as most patients will not require it.

In assessing the outcome of extended abdominal rectopexy, careful attention was paid to the functional results. Most of our patients had substantial pre-operative problems of constipation and incontinence, and this has been recorded by other authors[5,7,13,14]. Many patients were disappointed to find that their functional disabilities not only persisted, but were often aggravated by surgery. The incidence of intractable constipation was doubled post-operatively (to 47 per cent); in many patients incontinence persisted, although the overall figure was halved (to 19 per cent). Two lessons may be learned from these figures: (1) that we must study our patients more effectively before surgery to identify the nature of their colonic dysfunction[14]; (2) that if the functional problem is capable of surgical alleviation, this should be considered at the same time as the abdominal rectopexy. Muir[15] and Goldberg[4,16] have both combined left colonic resection with abdominal rectopexy, and it is likely that a selective approach would allow progress towards functional results to match the excellence of current anatomical repairs. Those patients who develop rectal prolapse as a result of neuromuscular deficits outside the bowel wall will always pose serious problems for functional correction. Finally, it was found that those patients ($n=8$) who come to extended abdominal rectopexy with a normal bowel habit had no problems of control postoperatively.

We surmise that the problem of rectal prolapse has now changed. As a result of improved technique, abdominal rectopexy can achieve anatomical cure in almost all (if not all) cases. What is needed now is a combined flexible approach to improve the functional results of surgery.

We conclude that abdominal rectopexy should continue to form the basis of surgical treatment and that lesser procedures[11,12,17-19] which are advocated on grounds of safety are not justified except in the most extreme circumstances. To subject a frail elderly patient to an operation that is almost certain to fail if she survives seems to be the worst possible choice that the surgeon can make.

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Tubercular fistula in ano

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Of 122 patients with fistulae in ano *operated upon in a 5-year period, 19 (15·6 per cent) were found to have tubercular fistulae on histopathological examination. There was no characteristic clinical picture and concomitant pulmonary tuberculosis was present in only three patients. Histological examination of the excised fistula is mandatory for the diagnosis of anal tuberculosis. There were no cases of Crohn's disease of the anal region.*

Keywords: Anal tuberculosis, fistula *in ano*

Tuberculosis of the anal region is so rare that during the last 15 years only isolated reports have appeared in the English literature[1–5], yet during the same period there has been a greater awareness of abdominal tuberculosis[6–9]. With the decline in the general incidence of tuberculosis, the incidence of anal tuberculosis has also shown a sharp decline from 16 per cent in 1921 to less than 1 per cent in 1969[10]. However, centres dealing with non-Europeans have reported an incidence as high as 17 per cent[11,12]. As excised fistulae *in ano* are not invariably subjected to histopathological examination, it may also be argued that some cases of tuberculous fistula are missed and the decline in the incidence may not be as sharp as reported. In view of this we have reviewed the case histories and the histological slides of 122 patients with fistula *in ano* treated during the preceding 5-year period.

Patients and methods

Retrospective analysis was carried out of the clinical features, and histological and bacteriological findings in 122 patients whose excised fistulae were subjected to histopathological examination. This number represents approximately 40 per cent of all the fistulae patients treated during the preceding 5 years in which histopathological examination was performed. The criteria for the diagnosis of anal tuberculosis was histopathological in that tuberculosis was incriminated if caseation necrosis, Langhans' giant cells and epithelioid infiltration were seen. The clinical features were analysed in retrospect after the diagnosis was made on microscopy.

Observations

Of the 122 fistulae, 19 (16 per cent) were tubercular. There were 18 males and 1 female with an age range of 16–55 years (median 31 years; 9 patients less than 30 years and 10 more than 30 years of age). The fistula was recurrent in 12 and was the first manifestation of tuberculosis in 7 patients. The mean duration of the fistula varied from 10 days to 5 years (mean 1·8 years). An anal discharge was present in all cases and perianal swelling in six (32 per cent). One patient had significant inguinal lymphadenopathy; in the remainder, inguinal lymph node enlargement was 'insignificant'. Constitutional symptoms of fever, anorexia and weight loss were not present in any patient. No patient had any chest complaint. Examination revealed a single fistula in 13 patients while 6 patients had multiple fistulae around the anal canal. The fistulae were high (internal opening at or above anorectal ring) in three and of the low type in the remaining sixteen patients; in addition, three patients had a posterior fissure *in ano*. Investigations showed absolute lymphocyte counts of over 2000/mm^3 in 8/19 patients and active pulmonary tuberculosis on straight chest radiograph in 3/19 patients. On histopathological examination of the resected fistulae, caseation necrosis, Langhans' giant cells and epithelioid cell infiltration was found in all 19 patients (*Figure 1*). Lymphocyte infiltration and fibrosis was also present in all cases. In six of the ten patients in whom acid-fast staining was carried out, the presence of *Mycobacterium tuberculosis* was demonstrated.

Discussion

There is no characteristic clinical picture for tubercular fistula *in ano*. In this series there was no difference in the clinical picture, including age and sex distribution and symptoms and signs of anal lesion, between the 19 cases of tubercular fistulae and the 103 cases of non-tubercular fistulae. Thus, if histological examination had not been carried out the diagnosis would have been missed. Abdominal tuberculosis is commoner in women[6] but only one of our 19 patients with anal tuberculosis was female. This reversal of the sex incidence is difficult to explain unless it is a simple reflection of a generally higher incidence of fistula *in ano* in male patients. It is interesting that hidradenitis suppurativa of the perianal region also shows a comparable reversal of sex incidence when compared with the disease in other sites.

The diagnosis of anal tuberculosis is difficult. The most important differential diagnosis is from anal lesions of Crohn's disease (*Table 1*). Anal fistulae are not a primary manifestation of Crohn's disease. They usually occur secondary to an anal fissure or a cavitating ulcer. They may also occur coincidentally with Crohn's disease of the gut[13]. Histological differentiation of Crohn's disease from tuberculosis depends upon the presence of caseating granulomas in the latter. The presence of acid-fast bacilli, although rare, is also diagnostic[10,14]. However, the use of antitubercular drugs can modify this picture and caseation may be absent. When this is the situation, response to specific chemotherapy will confirm the diagnosis[5]. Other less common conditions which may be confused with anal tuberculosis are venereal lesions, neoplasms, foreign body lesions and granuloma pyogenicum[14,15]. Anal tuberculosis can be diagnosed accurately only by the presence of caseation necrosis or epithelioid reaction on histology and/or the demonstration of acid-fast bacilli. Supportive evidence may be seen in the form of concomitant pulmonary tuberculosis and by a good response to a test dose of antitubercular drugs[5,11]. The appearance of the lesion is not characteristic but recurrence (non-healing) of the fistula after previous treatment should arouse suspicion. In 63 per cent of our patients the fistula was recurrent. In view of the high percentage of recurrent (non-healing) fistulae we recommend the use of antitubercular drugs in all patients with fistulae histologically proven to be tubercular. The presence of concomitant pulmonary tuberculosis points to the tubercular nature of the lesion but only about 1 per cent of the 0·8 per cent of patients who develop abdominal tuberculosis in the presence of pulmonary tuberculosis, develop anal tubercular lesions[16]. Although in 16 per cent of our cases pulmonary tuberculosis was associated with anal tuberculosis, a review of recent literature indicates a much lower incidence of this association[6,9].

Different morphological forms of anal tuberculosis, namely

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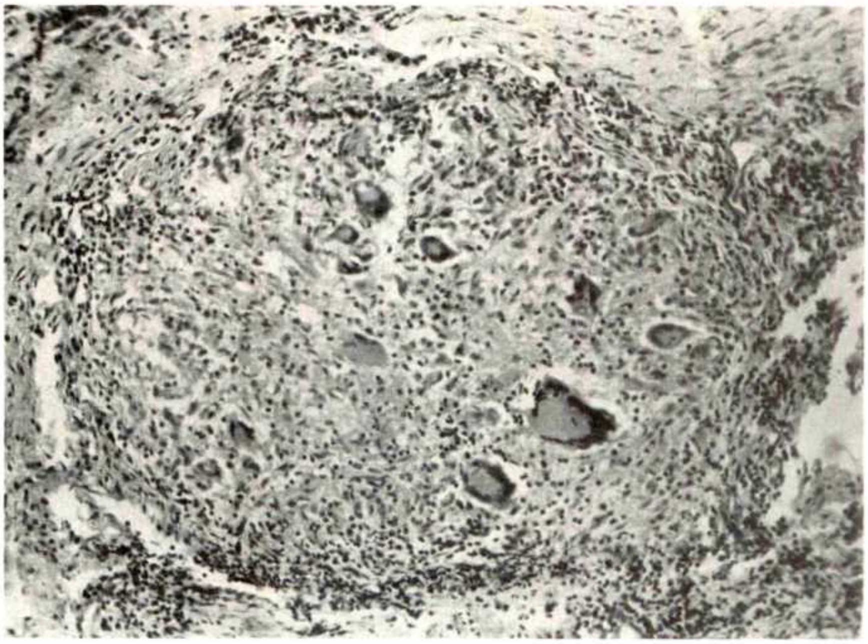

Figure 1 *Histopathology of excised fistula showing granuloma formation (× 50)*

Table 1 *Differences between anorectal lesions of tuberculosis and Crohn's disease*[10]

	Crohn's disease	Tuberculosis
Age	Teenage upwards	Over 30 years
Sex	Equal	Commoner in men
Appearance	Non-specific or typical	Usually non-specific
Chest radiograph	Usually no tuberculosis	Normally tuberculosis (old) or active tuberculosis
Mantoux test	No relationship	Always positive 1:100
Gastrointestinal disease	Sometimes present	Never
Histology	(1) Sarcoid or (2) Non-specific	(1) Caseating tubercular (2) Sarcoid or (3) Non-specific Acid-fast bacilli very rare
Culture for tuberculosis	Negative	Negative or positive
Guinea-pig inoculation	Negative	Negative or positive
Response to chemotherapy	No response	Improvement
Follow-up	May recur locally. May develop gastrointestinal Crohn's disease	Remains healed. No gastrointestinal changes

ulcerative, verrucous, lupoid and miliary, have been described[2,3]. None of these forms were encountered in our series, reflecting the overall change which has taken place in the manifestation of abdominal tuberculosis due to the widespread use of antitubercular drugs in this part of the world. The type of tubercular fistula *in ano*, though predominantly low in our cases, is usually a high fistula in the majority (57–58 per cent)[17].

In conclusion, tubercular fistula *in ano* is seldom diagnosed pre-operatively on the basis of the clinical picture. Multiple fistulae, recurrence of the fistula, presence of concomitant pulmonary tuberculosis and inguinal lymphadenopathy should arouse suspicion. In parts of the world where tuberculosis still prevails and in all cases of multiple and recurrent fistula *in ano*, histopathological examination of the excised fistulous tract is mandatory.

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40–43

Assessment of microtransducers in anorectal manometry

It has been reported that microtransducer-tipped catheters (transducer) produce reliable reproducible measurements which correlate well with water-filled balloon systems. Maximum resting pressure (MRP) and maximum voluntary contraction pressures (MVC) were compared using a standard station pull-through technique in 12 patients. There was a poor correlation for both MRP: microballoon, 115 cmH_2O (60–160 cmH_2O); transducer 60 (20–110), r = 0·62, P < 0·05, *and MVC: microballoon, 202 (60–375); transducer, 175 (60–210),* r = 0·42, *n.s. To determine whether this was due to radial variation in pressures measured by the transducer, we studied a further 39 patients with both systems. At each station, transducer measurements were made at each of four quadrants. We found better correlation for MRP: microballoon, 100 (40–175); transducer, 66 (34–120),* r = 0·72, P < 0·001, *and MVC: microballoon, 225 (55–650); transducer, 180 (50–470),* r = 0·87, P < 0·001, *but a significant radial variation for the transducer where rotation reduced MRP pressure measurements by 21 per cent (0–600 per cent), and MVC 17 per cent (0–76 per cent). Moreover there was a significant difference between anterior and posterior MRP in the upper anal canal, anterior 35 (5–80)* versus *posterior 25 (10–60),* P < 0·05. *These results account for the poor correlation between random positioning of the microtransducer-tipped catheter and indicate that radial orientation must be taken into account.*

Keywords: Microtransducer, anorectal manometry

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Manometry is fundamental to physiological assessment of the anorectum but a multiplicity of systems are currently in use, making comparison between centres difficult and often producing conflicting results[1]. Conventional manometry depends on a water-filled tube conducting pressure changes from the sensing probe to an external transducer, but microtransducers are now available that can be fitted into fine catheters, thus eliminating the need for water-filled tubing and all the associated problems. Ambient pressure is conducted via a plastic membrane to an ultra-thin metal diaphragm, which in turn is connected to a strain gauge. The whole assembly is supported by a cradle surrounded by a steel cylinder and mounted in a silastic catheter, often as narrow as 2 mm in diameter. The pressure-sensitive membrane of these microtransducer-tipped catheters, however, is not circumferential (*Figures 1* and *2*). Radial variation in anal canal pressure has been shown[2,3], particularly in the region of the puborectalis sling and it is possible, therefore, that these catheters could record varying pressures with different radial orientation of the tip. A recent study[4] has reported good correlation between the microtransducer and conventional water-filled manometry. This study used the continuous pull-through technique with the microtransducer and the station pull-through with the water-filled system. The aim of the study described here was to compare the results obtained with microtransducers with those of conventional water-filled microballoon manometry and to determine whether any discrepancy between them could be accounted for on the basis of radial pressure variation.

Patients and methods

The microballoon system consisted of a 6 mm water-filled latex balloon (Precision Dippings Ltd, Bristol, UK) connected via indistensible tubing to an external transducer (Statham P23 Gb, Spectromed Ltd, Coventry, UK). The whole system was flushed with water to remove air bubbles and was leak free. The transducer output was recorded on a multichannel recorder (Hewlett Packard 7888A, Massachusetts, USA). The microtransducer-tipped catheter used was a Gaeltec 16CT/Sil 3 (Gaeltec Ltd, Dunvegan, Isle of Skye, UK) connected to a Dantec 21C15 amplifier and System 2100 recorder (Dantec Electronics, Bristol, UK). Each system was calibrated to 100 cmH_2O before use and all studies were carried out with the patient in the left lateral position without any bowel preparation. An indelible mark was made at the anal verge and all measurements were made from this point. The station pull-through technique was used with both systems, each catheter being placed 6 cm into the rectum and withdrawn at 0·5 cm intervals until the high-pressure zone was reached. Thereafter the maximum resting pressure (MRP) and maximum voluntary contraction pressure (MVC or 'squeeze pressure') were measured at 1 cm stations from the anal verge.

Study 1

In an initial study, 12 patients with a variety of anorectal disorders had manometry performed with both systems. The microtransducer was placed with no regard to its radial orientation.

Study 2

Thirty-nine patients, thirty controls and nine with idiopathic faecal incontinence were studied. Microballoon manometry was performed first, followed by measurements with the microtransducer; measurements of MRP and MVC were taken with the microtransducer facing each of four quadrants (anterior, posterior, left, and right) at every station. Ten seconds were allowed between each measurement of MVC to prevent error due to muscle fatigue. The highest figure from all the recordings with the microtransducer was taken as the MRP and MVC and this was correlated with the value from the microballoon system.

Statistical analysis

The Rank Spearman correlation coefficient was used to correlate results from the two systems and the Mann–Whitney *U* test was used to compare results of radial variation with the microtransducer.

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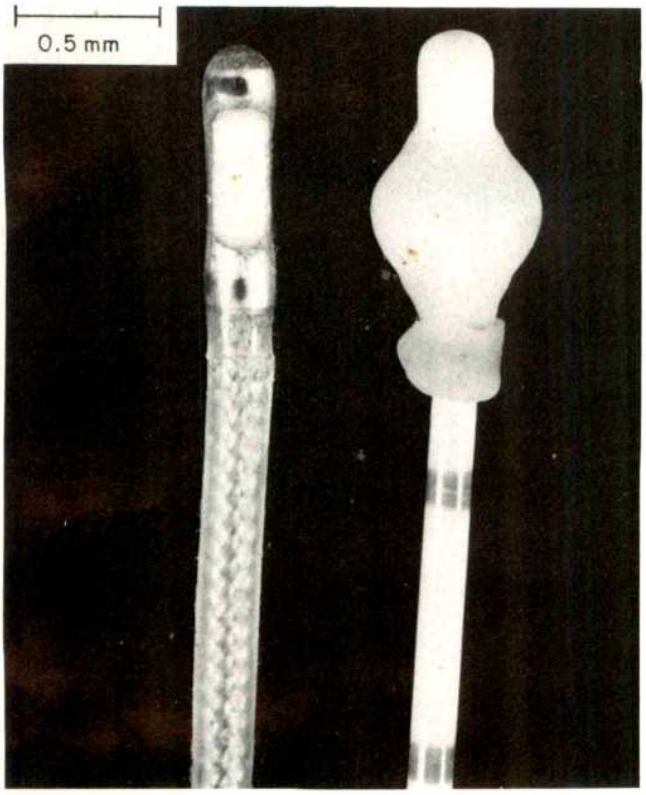

Figure 1 *The microtransducer (left) and microballoon manometry catheters*

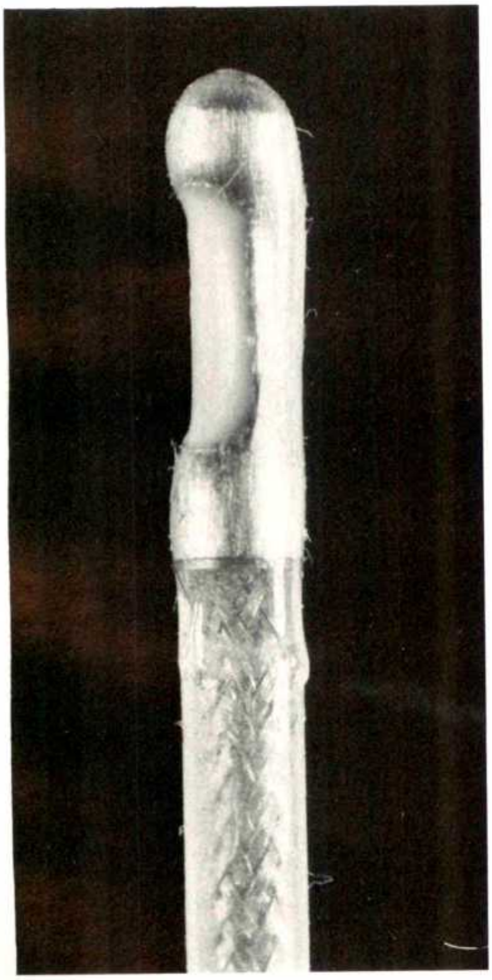

Figure 2 *Side view of the microtransducer catheter tip. The white sensing membrane can be seen facing one direction only*

Results

Study 1

There was a poor correlation for MRP: microballoon, median 115 cmH_2O (range 60–160 cmH_2O); microtransducer, 60 cmH_2O (range 20–110 cmH_2O), $r=0{\cdot}62$, $P<0{\cdot}05$. Poor correlation was also found for MVC: microballoon, median 202 (range 60–375); transducer, median 175 (range 60–210), $r=0{\cdot}42$, n.s. (*Figure 3*).

Study 2

Using this more detailed method a much improved correlation was obtained for MRP: microballoon, median 100 cmH_2O (range 40–175 cmH_2O); microtransducer, median 66 (34–120), $r=0{\cdot}72$, $P<0{\cdot}001$. Similarly, improved correlation was found for MVC: microballoon, median 225 cmH_2O (range 55–650 cmH_2O); microtransducer, median 180 (range 50–470), $r=0{\cdot}87$, $P<0{\cdot}001$ (*Figure 4*).

There was, however, considerable radial variation at the

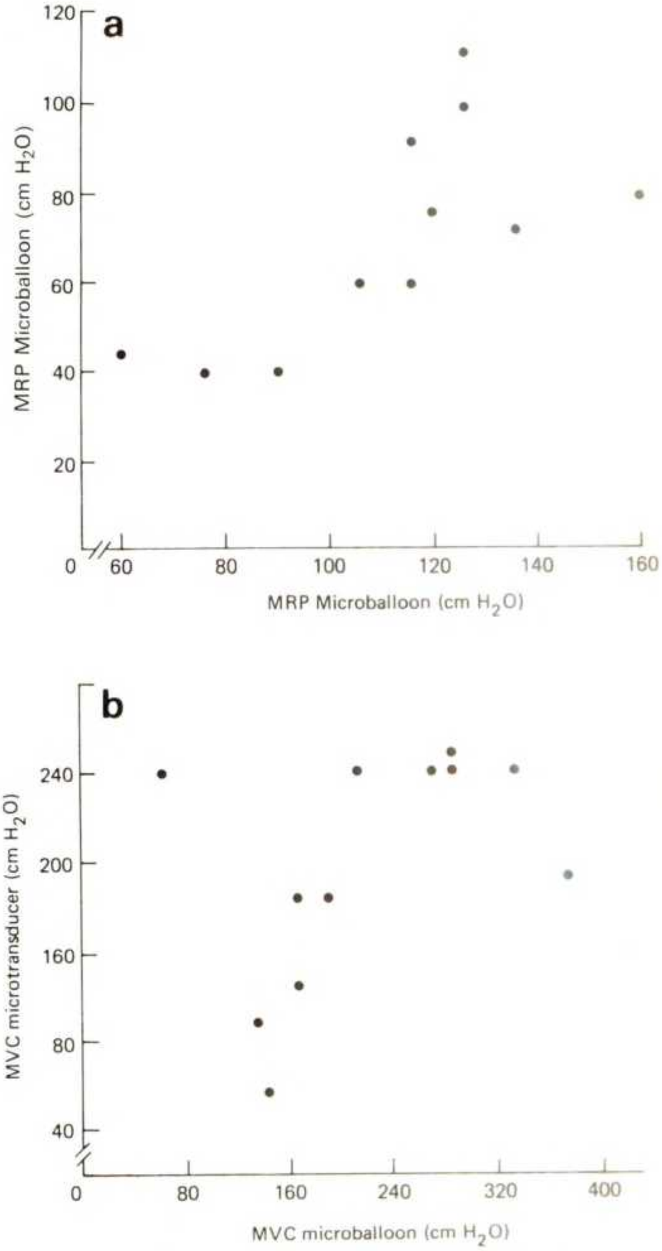

Figure 3 *Correlation of microtransducer* versus *microballoon results with random radial positioning of the microtransducer.* n = *12. (a) MRP* $r=0{\cdot}62$, $P<0{\cdot}05$; *(b) MVC* $r=0{\cdot}42$, *n.s.*

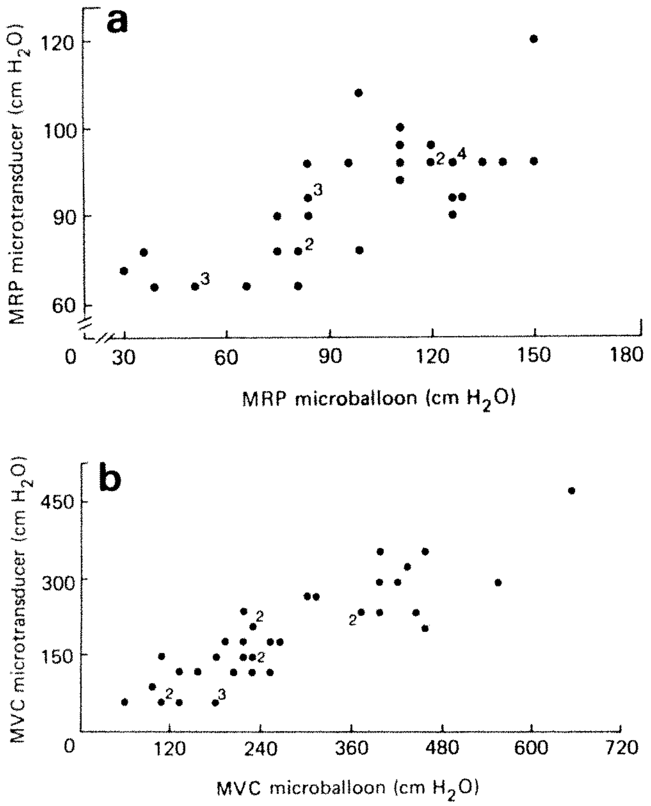

Figure 4 *Four quadrant microtransducer results correlated with microballoon manometry.* n=*39*. (*a*) *MRP* r=*0·72*, P<*0·001*; (*b*) *MVC* r=*0·87*, P<*0·001*. (*Numbers indicate points of superimposition of identical results*)

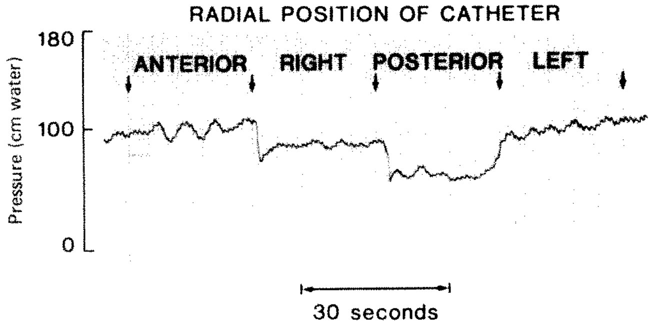

Figure 5 *Radial variation of MRP*

station at which the MRP and MVC was recorded (median variation MRP 21 per cent, range 0–600 per cent, median variation MVC 17 per cent, range 0–76 per cent) (*Figures 5* and *6*). In addition there was a significant anterior *versus* posterior difference in MRP in the upper sphincter, the higher pressure recorded being anterior ($P < 0{\cdot}05$, *Figure 7*). There was no difference in sphincter length as measured by the two systems, except when the microtransducer faced posteriorly. In this position the sphincter length was significantly shorter than that measured by the microballoon ($P < 0{\cdot}05$), and also shorter than the length measured with the transducer facing anteriorly ($P < 0{\cdot}05$).

Discussion

Water-filled systems are the commonest method of anorectal manometry currently in use. They employ either an open-tipped perfused probe or a microballoon as the pressure-sensitive device connected to an external transducer. Both are prone to artefacts produced by movement of the tubing and air in the

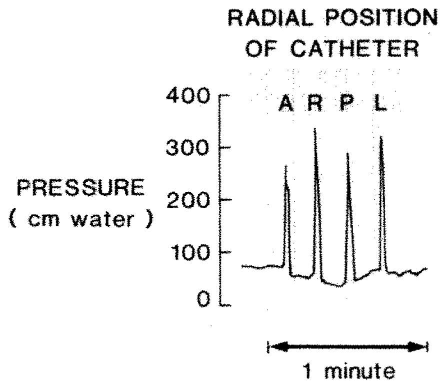

Figure 6 *Radial variation of MVC*

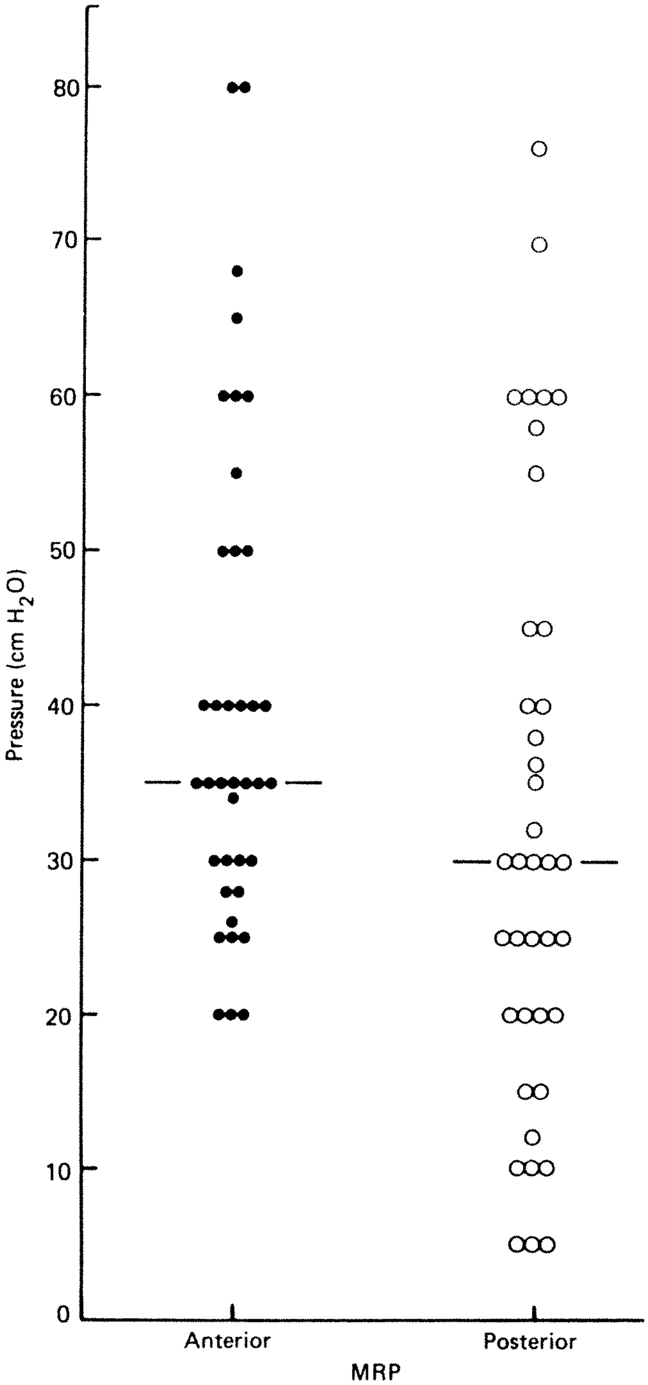

Figure 7 *Anterior* versus *posterior pressure in the upper sphincter recorded by the microtransducer*, P<*0·05*

system and both record higher pressures if a larger-diameter probe or balloon is used[3,5,6]. Other variables which alter the recorded pressure from the perfused system include the rate of perfusion[7] and the site of the openings[8]. It has also been argued that the inevitable leakage of fluid from the perfused probe on to the perianal skin could stimulate the sphincter[9].

Attempts have been made to measure the radial force in the anal canal with strain gauges[10,11] but such systems are fragile and are not suitable for routine use. Microtransducers have the advantage of small size (which accounts for the lower pressures recorded with them in this study), and the absence of any fluid-filled part to the system eliminates artefacts. As a consequence several reports have advocated their use[4,12–14]. They are, however, much more expensive than external transducers and are prone to damage. We have shown in this study that in the anal canal they display considerable radial variation in pressure and that, using the standard station pull-through technique, their results do not correlate well with a conventional water-filled microballoon system. This problem can be overcome by taking several readings at each station but at the expense of time and convenience. Unfortunately, the direction at which the highest MRP and MVC value were recorded (i.e. those which correlated well with the microballoon) were located at random positions, making several recordings at each level necessary.

Catheters are available with several radially arranged microtransducers recording multiple pressures at each station, but their cost is prohibitive for general use. The good correlation reported by Varma and Smith[4] may be due to the infinite number of 'stations' that are recorded using the continuous pull-through technique, thereby increasing the chance of a high value being recorded. There is, however, a distinct possibility when using this technique that the movement of the probe in the anal canal stimulates the sphincter, producing erroneous results. Varma and Smith, however, found no difference in pressure when the catheter was stationary, compared with when it was moving.

Our finding of a higher resting pressure anteriorly in the upper anal canal conflicts with previous reports in which rigid catheters were used[2,11]. Such rigid catheters would resist the forward pull of the puborectalis and hence would record artificially high pressures. Radial pressure variation within the anal canal has also been investigated by Penninckx[15]. He used a 4 mm catheter with three microtransducers arranged at 120 degree intervals round its circumference but at differing levels. He found a higher pressure posteriorly and laterally in the upper anal canal in a group of 20 patients. No consistent variation was found in the lower anal canal. The high posterior pressure may be attributable to the larger diameter and relative inflexibility of the catheter. It is likely that the very flexible catheter used in this study allowed the forward pull of the puborectalis muscle to force it against the anterior anal canal wall, thereby increasing the pressure recorded when the transducer faced anteriorly. It is to be expected that, as a result of the relatively low posterior pressure recorded in the upper anal canal in this study, the length of the high-pressure zone would be shorter in this position, which was indeed the case.

In conclusion, we suggest that the solitary microtransducer is not suitable for station pull-through anorectal manometry unless error due to radial variation is taken into account.

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Anorectal sampling: a comparison of normal and incontinent patients

It has been suggested that sampling of rectal contents by the anal canal may play a role in the continence mechanism. To investigate this concept we studied 18 patients with faecal incontinence and 18 age and sex matched controls. A microtransducer catheter was positioned so that pressures were recorded from the rectum, the junction of the upper and middle thirds of the anal canal and the lower anal canal. Recordings were taken at rest and while distending the rectum with air in a balloon, and then with air injected freely into the rectum. Sampling (equalization of the rectal and upper anal canal pressures) was seen to occur spontaneously in 16 of the controls and only 6 of the incontinent group ($P<0.02$) and induced sampling occurred at a higher rectal volume in the incontinent group than in controls for freely injected air ($P<0.002$). Defective anorectal sampling may be an important contributory factor in the pathogenesis of anorectal incontinence.

Keywords: Anorectal sampling, incontinence

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The anal canal has been shown to have a rich sensory innervation[1]. In 1963 Duthie and Bennett[2] demonstrated that the upper anal canal relaxed sufficiently in response to rectal distension for rectal contents to come into contact with this sensitive epithelial lining. They considered that this 'sampling' response could have a role in the continence mechanism by providing accurate sensory information about the nature of rectal contents, allowing discrimination between flatus and solid stool.

It was the aim of this study to clarify the role of this response in the continence mechanism. Our aim was to determine whether it occurred spontaneously, define the minimum volume of rectal distension that elicited the response, and see whether it was normally present in patients with incontinence.

Patients and methods

Tests were carried out on 18 incontinent patients, 14 women and 4 men, median age 53·5 years (range 18–86). They had all undergone the relevant clinical examinations and investigations. Incontinence followed surgery for high fistulae in two men; the remainder had idiopathic faecal incontinence. Fourteen were incontinent to a fluid stool with only four being incontinent to both fluid and solid stool. The controls were patients admitted for routine surgery unrelated to the alimentary tract and were matched for age and sex. They had no anorectal complaints. The obstetric data of the female patients from both groups is given in *Table 1*.

Design of study

The studies were performed in the left lateral position. No specific preparation was used apart from giving the patients the initial opportunity of emptying their bowel. Digital and proctoscopic examination of the rectum and anal canal was first performed in all cases to exclude occult anorectal disease. The sampling reflex was then studied followed by tests of anorectal sensation.

Anorectal manometry

A special microtransducer manometric system was used to minimize disturbance of the anorectum. It consisted of three microtransducers mounted on a flexible silastic catheter, 2 mm in diameter (Gaeltec Ltd, Skye, UK). One microtransducer was mounted at the tip, the second and third being 4 cm and 6 cm, respectively, proximal to this. The catheter was inserted into the rectum and a delay of a few minutes allowed for the sphincter pressures to return to normal. A mark was made on the skin near the anal verge and all subsequent measurements were made from this point. A careful station pull-through was then performed, taking into account radial pressure variation, to determine the sphincter length. The catheter was then placed with the transducers facing laterally so that the tip was in the rectum and the middle microtransducer recorded the pressure from the junction of the middle and upper thirds of the anal canal. It was taped securely in position with 'elastoplast' up to the anal verge and the patient remained still throughout the study. The lowest microtransducer usually recorded the pressure in the lower anal canal except in the few patients in which the sphincter was 2 cm or less in length so that the microtransducer projected from the anal verge.

'Sampling' was defined as the point at which the rectal pressure was equal to or greater than that in the upper anal canal. The middle microtransducer was placed at the lowermost limit of the upper zone of the anal canal as sensation was measured in zones (*see below*). This ensured that the entire upper zone was at rectal pressure or less when 'sampling' occurred.

Pressures were recorded for 5 min at rest or until spontaneous sampling occurred, whichever was the shorter period. The balloon used for rectal distension was made from thin latex and measured 6 cm by 5 cm when inflated by 100 ml of air. It was inflated by a catheter (external diameter 1·5 mm) and was inserted into the rectum so that its proximal extent was 10 cm from the anal verge. After a delay of a few minutes it was inflated by 10 ml of air at room temperature from a syringe. If sampling did not occur within 10 s it was deflated and reinflated, increasing the volume injected by 10 ml each time until sampling occurred or 100 ml was reached. The balloon was removed and a fine catheter (external diameter 1·5 mm) inserted so that the tip was midway between the rectal and upper anal microtransducers. Air was injected into the rectum via this catheter in 10 ml increments, again waiting 10 s for sampling to occur. The maximum volume injected was 100 ml.

Sensory tests

Fifteen of the control patients and all the incontinent patients had anal sensation assessed in the lower, middle and upper zones by mucosal electrosensitivity. A narrow catheter with two platinum electrodes 1 cm apart on its surface was used. This was introduced into the anal canal and a small current passed between the electrodes from a constant

Table 1 *Details of obstetric history in 14 female patients with incontinence*

	Average parity	Perineal tears (%)	Forceps delivery (%)	Hysterectomy (%)
Control	1·5	40	13	20
Incontinent	2·2	80	60	20

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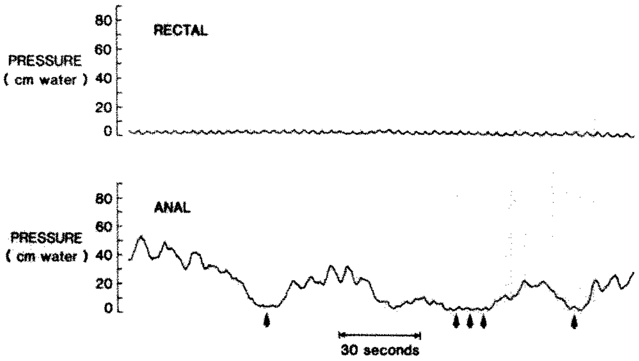

Figure 1 *Spontaneous sampling with no increase in rectal pressure. Arrows indicate points at which sampling occurred*

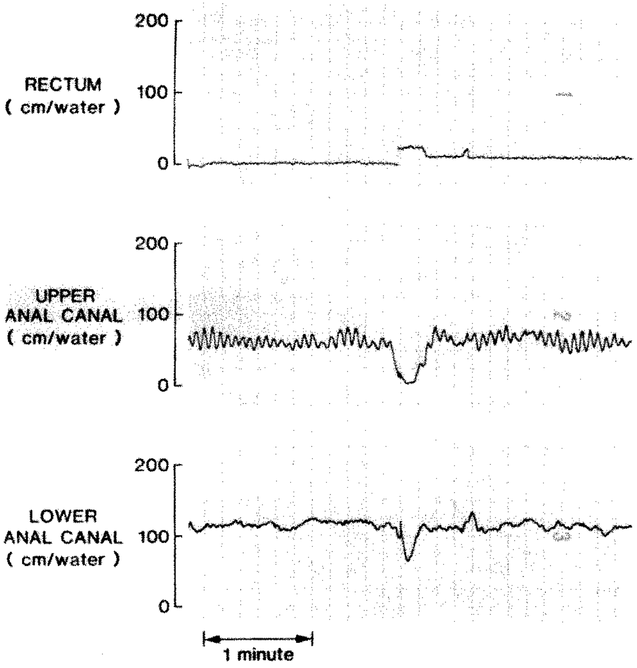

Figure 2 *Spontaneous sampling associated with a rise in rectal pressure*

current generator (Department of Medical Physics, Bristol Royal Infirmary). The current was increased by increments of 1 mA until the patient felt a sensation which was often described as tingling or pulsing. An average of three recordings at each level was taken as the threshold value. In addition, thermal sensitivity was assessed in all controls and 15 incontinent patients in the same zones of the anal canal. A water perfused thermode, 1 cm long and 1 cm in diameter was used in the same zones that had had mucosal electrosensitivity testing. The thermode temperature was held at 37°C and then increased or decreased by 4·5°C so as to provide a hot and cold stimulus at precise 1 cm zones of the anal canal. The patient informed the investigator of any temperature change felt during four temperature shifts, normal to hot, hot to normal, normal to cold and cold to normal. From the trace of temperature change, four values of the minimum detectable temperature change (MDTC) could be measured and a median of these was taken to represent thermal sensitivity at each level. These techniques have been described in detail previously[3,4].

Ethical considerations

The study was approved by the Ethical Committee of the Bristol and Weston Health Authority and each patient gave their informed consent.

Statistical analysis

The χ^2 test was used to compare the relative frequencies of spontaneous sampling in the two groups. To compare the results of volumes and pressures at which sampling occurred, the Mann–Whitney *U* test was used.

Results

Spontaneous sampling occurred in 16 (89 per cent) of the control patients. In nine patients it occurred with no discernible increase in rectal pressure (*Figure 1*); in the remaining seven patients there was an associated increase in rectal pressure that preceded the fall in anal canal pressure (*Figure 2*). The patient had no conscious appreciation of this phenomenon.

In the incontinent group spontaneous sampling occurred in six patients. This difference was significant ($P<0{\cdot}02$, χ^2 test). Sampling induced by air injected freely into the rectum is illustrated in *Figure 3*. It occurred at a lower volume in the controls (median 10 ml; range 10–70 ml) than in the incontinent patients (median 40 ml; range 10–$>$100 ml). There was no difference when air was injected into the balloon—control: median 20 ml; range 10–70 ml; incontinent: median 20 ml; range 10–70 ml. There was no significant difference between the two groups in the rectal pressure change associated with sampling for spontaneous or induced sampling although there was a trend to a higher pressure for sampling induced by injection of free air in the incontinent group. The injection of free air was often felt by the control patients but there was less conscious appreciation of rectal distension, either with free air or the balloon, in the incontinent group.

Both mucosal electrosensitivity and thermal sensitivity results in the control patients were very similar to those we have previously published[3,4]. Controls were highly sensitive to thermal stimuli at all levels of the anal canal but this was severely impaired in the incontinent group (*Table 2*). Similarly, mucosal electrosensitivity was significantly worse in the incontinent patients in the middle and upper zones of the anal canal but not in the lower zone. This perhaps reflects the mild degree of incontinence in the group as a whole. Differences were more pronounced in the upper anal canal. *Table 2* shows the detailed results of sensory testing.

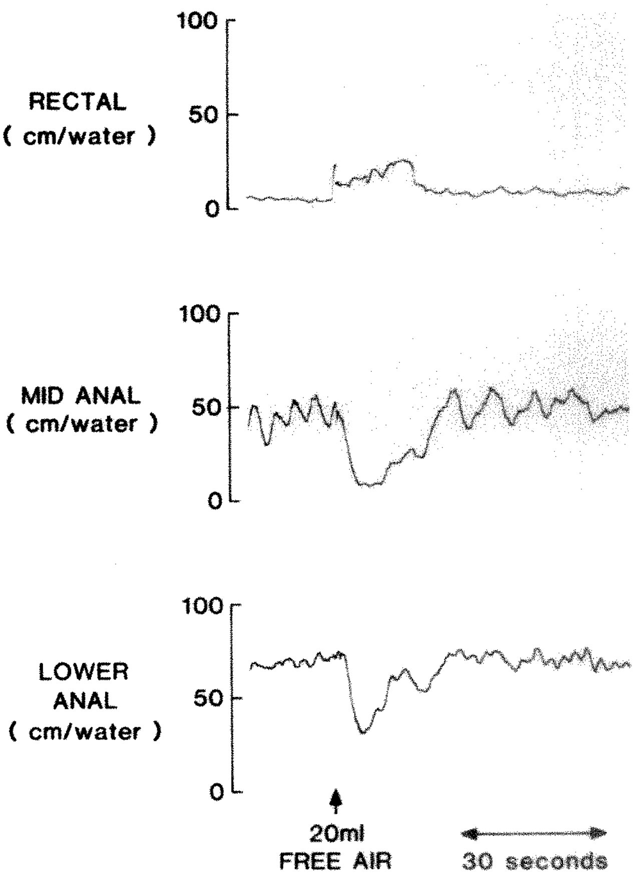

Figure 3 *Sampling induced by the injection of 20 ml of air freely into the rectum. In this example the anal pressure was recorded from the mid-zone*

Table 2 *Results of sensory tests in control and incontinent patients*

Test	Zone of anal canal	Control	Incontinent	P value*
Electro-sensitivity (mA)	Lower	4 (3–6)	5 (4–8)	n.s
	Middle	3 (2·5–5)	6 (5–8)	0·002
	Upper	5 (4–7·5)	11 (7–19)	0·0001
Thermal sensitivity (median MDTC, °C)	Lower	0·9 (0·6–1·1)	1·9 (1·2–2·5)	0·001
	Middle	0·9 (0·8–1·3)	1·6 (1·4–2·8)	0·0001
	Upper	1·0 (0·75–1·9)	>4·5 (3·6–>4·5)	0·0001

* Mann–Whitney *U* test; MDTC, minimum detectable temperature change

Discussion

Continence is maintained by a number of factors and while there is broad agreement on the structures and organs involved there are differences in opinion regarding their mechanism of action[5]. The voluntary sphincters are of prime importance as they are continuously active and reflexly contract in response to increased intra-abdominal pressure[6], thereby preventing faecal leakage during activities such as coughing. At rest, however, they contribute only 15–30 per cent of the anal canal pressure, the majority of pressure being generated by the internal anal sphincter[7,8]. It would appear that the internal sphincter provides a basal pressure which is augmented by the external sphincter muscle either voluntarily or reflexly as required. Incontinent patients usually have a reduction of both resting and maximum 'squeeze' pressures[9] although we have seen incontinence associated with a profound impairment of either in isolation.

The role of the puborectalis muscle and the angle it produces between the anal canal and the rectum has been emphasized. According to this theory continence is maintained by the anterior rectal wall being forced down into the upper anal canal by increases in intra-abdominal pressure[10]. More recently, however, it has been demonstrated by visualizing the anorectum videographically during a Valsava manoeuvre that this does not occur[11]. Also several authors have demonstrated that the operation of postanal repair, designed to improve continence by recreating an acute anorectal angle, has no significant effect on the angle and yet is successful in approximately 60 per cent of cases while a further 15 per cent are significantly improved[12,13].

Many other factors undoubtedly play a part in maintaining normal continence. Rectal sensibility[14], reverse gradients of activity in the rectum[15] and anal canal[16], and in particular a normal compliant rectum[17,18], probably all make a contribution. The role of anal sensation is less clear. Anal relaxation induced by rectal distension was demonstrated by Gowers[19] as long ago as 1877 but Duthie and Bennett were the first to show that in the upper anal canal this relaxation could be sufficient to allow rectal contents to come into contact with sensitive anal mucosa[2]. In 19 male control subjects they measured first the proximal extent of anal sensation with a fine bristle. Using a non-perfused water-filled manometric system rectal pressure was continuously measured and a station pull-through anal sphincter profile performed before and during distension of the rectum with 100 ml of air in a balloon. They found that the rectal pressure reached the sensitive anal mucosa in 13 of 17 patients in whom complete data were available, such that up to 2 cm of sensitive mucosa was exposed.

In this study anal sensation was tested objectively by our new methods of mucosal electrosensitivity and temperature sensation. Electrocutaneous stimulation activates large and small myelinated afferents from gut mechanoreceptors[20]. While mechanosensitivity is important there is general agreement amongst sensory physiologists that the temperature sense plays a fundamental role in the discrimination between gas, liquid and solid and in particular the sensation of 'wetness'. In normal skin this is a blended sensation dependent on both tactile and thermal stimuli. Objective evidence for this is derived from patients in whom the spinothalamic tract is cut in the treatment of intractable pain. Following this procedure thermal sensitivity is lost and tactile sensation is retained but they lose the sensation of 'wetness'[20]. We have described previously the high degree of thermal and mucosal electrosensitivity in the normal anal canal and the profound reduction in patients with idiopathic faecal incontinence which reduces their ability to discriminate the nature of rectal contents.

The results of this study further emphasize the role of sensory information in the continence mechanism. We suggest that in health the anal canal regularly relaxes subconsciously allowing the sensitive mucosa to come into contact with rectal contents giving continuously updated information to the spinal cord. This phenomenon was less frequently observed in the incontinent patients who were as a result deprived of important sensory information. Sampling also occurred at lower thresholds for air freely injected into the rectum in controls compared with incontinent patients and this would also tend to blunt sensory information from the region. These patients therefore have two factors which are likely to impair their discriminatory ability. Firstly, they have severely reduced sensation in the anal canal and secondly their defective sampling response diminishes the chance of rectal contents coming into contact with it. This would explain frank incontinent episodes of which many patients are completely unaware.

Distension of the rectum by air instilled within a balloon as opposed to freely into the lumen did not reveal any differences between the groups. The reason for this is obscure but it is possible to speculate that the inevitably slower distension involved in inflating the balloon stimulated a different set of stretch receptors that were unaffected by the neuropathic process in idiopathic faecal incontinence.

In conclusion, we have confirmed the existence of the sampling response and shown that it occurs at much lower volumes of rectal distension than originally thought. In addition, incontinent patients have a dual defect in the sensory arm of the continence mechanism which in part explains the difficulties of these patients and has implications for their management.

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Case reports

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Testicular torsion after previous orchidopexy

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Testicular torsion after previous bilateral orchidopexy is rare; eighteen cases have been reported during the last two decades[1–7]. The majority of patients had recurrent torsion (or torsion contralaterally) following previous surgical fixation. We present two cases of testicular torsion where orchidopexy was performed years earlier for non-descended testes.

Case reports

Case 1

A 34-year-old man, who had undergone left orchidopexy 17 years earlier because of a non-descended left testicle, was admitted to hospital with a 4 h history of sudden, severe and constant pain of the left scrotum accompanied by nausea, vomiting and slightly increased temperature. On examination, the genitalia showed moderate diffuse swelling. Tenderness was most pronounced over the epididymis which was located in a normal posterior position. The condition was regarded as acute epididymitis and treated with antibiotics. By the following day the temperature was normal and the pain decreased, but the swelling was slowly enlarging and surgery was performed on the fourth day.

The left testis and epididymis were dark, cyanotic and haemorrhagic. The torsion was located at the earlier fixation site between the tail of the epididymis and the scrotal wall. The operation report of the initial orchidopexy was examined, but did not reveal any detail about the fixation procedure or kind of suture material.

Case 2

A 26-year-old man was admitted with a 24 h history of sudden right scrotal pain with radiation to the right groin. The patient had undergone right orchidopexy for an undescended testicle 15 years earlier. On examination the testicle was found in a transverse position high in the scrotum. Tenderness was diffuse and the epididymis swollen.

At immediate exploration the testis was rotated 720 degrees and the proximal third was cyanotic and of doubtful viability. However, the testis was salvaged and fixed to the dartos. The original orchidopexy had been carried out with fixation of the testicle to the bottom of the scrotum with two catgut sutures.

Discussion

Torsion of a previously fixed testicle is reported rarely[1–7], but this does not reflect its true incidence. In only three reported cases[1,7] had the original fixation been performed because of a non-descended testicle.

The basic method of testicular fixation must create permanent adherence between the testicle and the scrotal wall. Joehenning[1] and Whitaker[8] have reviewed several different surgical methods of orchidopexy, reflecting difficulty in defining an optimal surgical procedure. Most investigators recommend one or two sutures between testicle and scrotal wall. By leaving the testicular serosal covering intact and suturing the testicle to a parietal serosal surface, often by the use of absorbable suture material, the expected fibrosis may be too weak. According to experimental data[5], the best adherence is achieved by creating a window in the tunica vaginalis, allowing broad contact between the tunica albuginea and the scrotal wall. Non-absorbable suture material is recommended[2].

In conclusion, previous testicular surgery does not, as is often clinically regarded, guarantee permanent fixation of the testis, not even after bilateral orchidopexy. If clinical signs and symptoms indicate that torsion is a possible diagnosis, scrotal exploration is mandatory, regardless of previous testicular surgery.

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Prospective study of the effects of postanal repair in neurogenic faecal incontinence

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The most important factor associated with a good result in the surgical treatment of neurogenic faecal incontinence by postanal repair is considered to be restoration of the obtuse anorectal angle. Sixteen patients (14 F:2 M; median age 59 years) with neurogenic faecal incontinence confirmed by a raised fibre density in the external anal sphincter underwent postanal repair. Pre- and postoperative manometric assessment was performed in 16 and radiological assessment in 12. Normal ranges for these parameters were established in age and sex matched control subjects. Continence was improved in 14 (88 per cent) patients, 6 (38 per cent) of whom regained normal continence, at a minimum of 15 months follow-up. A successful outcome was associated with no significant change in basal (pre-operative 35 (10–85) cmH_2O, postoperative 44 (12–105) cmH_2O; n.s.) or voluntary (pre-operative 43 (5–150) cmH_2O, postoperative 32 (12–180) cmH_2O; n.s.) components of anal canal pressure. There was a small but significant increase in sphincter length (pre-operative 2 (0–3) cm, postoperative 2·5 (0–3·5) cm; $P<0.01$). There was no significant change in the anorectal angle at rest (pre-operative 96 (90–110) degrees, postoperative 107 (79–118) degrees; n.s.) in the patients in whom continence was restored and five of these patients had resting anorectal angles within the normal range (75–94 degrees). Thus postanal repair need not be restricted to patients with widening of the anorectal angle since its beneficial effects do not appear to be related to reduction of this angle.

Keywords: Postanal repair, faecal incontinence

The precise mechanism whereby the anal sphincters maintain faecal continence is not fully understood. It has been suggested that faecal incontinence is associated with reduced anal canal pressure[1,2], decreased sphincter length[3], and widening of the angle between the lower rectum and the anal canal[3–5]. Of these factors loss of anorectal angulation has received most emphasis because of its relationship to the flap valve theory of continence[6]. This states that as a result of the anorectal angle the anterior rectal mucosa abuts on to the top of the anal canal and occludes it during periods of raised intra-abdominal pressure. In the majority of patients with idiopathic faecal incontinence gradual denervation of the sphincter muscles causes them to become weak[7–9]. This condition has been termed neurogenic faecal incontinence; it is denervation of the puborectalis muscular sling which causes widening of the anorectal angle.

The operation of postanal repair was designed to correct the abnormalities identified in incontinent patients. It involves plication of the muscles of the pelvic floor and anal sphincter behind the anorectum with the aim of restoring anorectal angulation and increasing sphincter length[10]. The extent to which these aims are achieved is not entirely clear. Since the operation is not uniformly successful, it is important to understand the mechanisms which lead to a satisfactory outcome so that selection of patients can be improved. In this study we have measured radiological and manometric parameters, before and after postanal repair, in the hope of identifying the factors responsible for the restoration of continence.

Patients and methods

Patients

Sixteen patients (14 F:2 M), median age 59 years (range 44–86), with neurogenic faecal incontinence diagnosed by clinical examination and raised puborectalis fibre density, and 14 age and sex matched control subjects (13 F:1 M), median age 59 (41–83) were investigated. The control subjects were volunteers, free from anorectal symptoms, admitted to hospital for minor surgical procedures. Incontinence was graded as follows: Grade A, continent to solid and liquid stool and flatus; Grade B, continent to solid and liquid stool but not to flatus; Grade C, continent to solid stool but not to liquid stool or flatus; Grade D, incontinent to solid and liquid stool and flatus. Patients with Grades A and B had no faecal leakage, whereas leakage tended to be intermittent in Grade C and more or less continuous in Grade D. Patients who achieved Grades A and B after surgery were considered to have had a successful outcome.

This study was approved by the Ethical Committee of the General Infirmary at Leeds in December 1982. All subjects gave their informed consent before taking part.

Methods

The subjects underwent a series of manometric, electromyographic and radiological investigations. No bowel preparation, other than a request for the subject to empty the rectum before testing, was used. A detailed description of our investigative techniques has previously been published[5]. Briefly the basal and voluntary components of anal canal pressure (*Figure 1*), representing internal and external sphincter function respectively[11,12], were determined by a station pull-through technique using a water-filled microballoon. The highest basal and voluntary pressure increments recorded along the anal canal were noted

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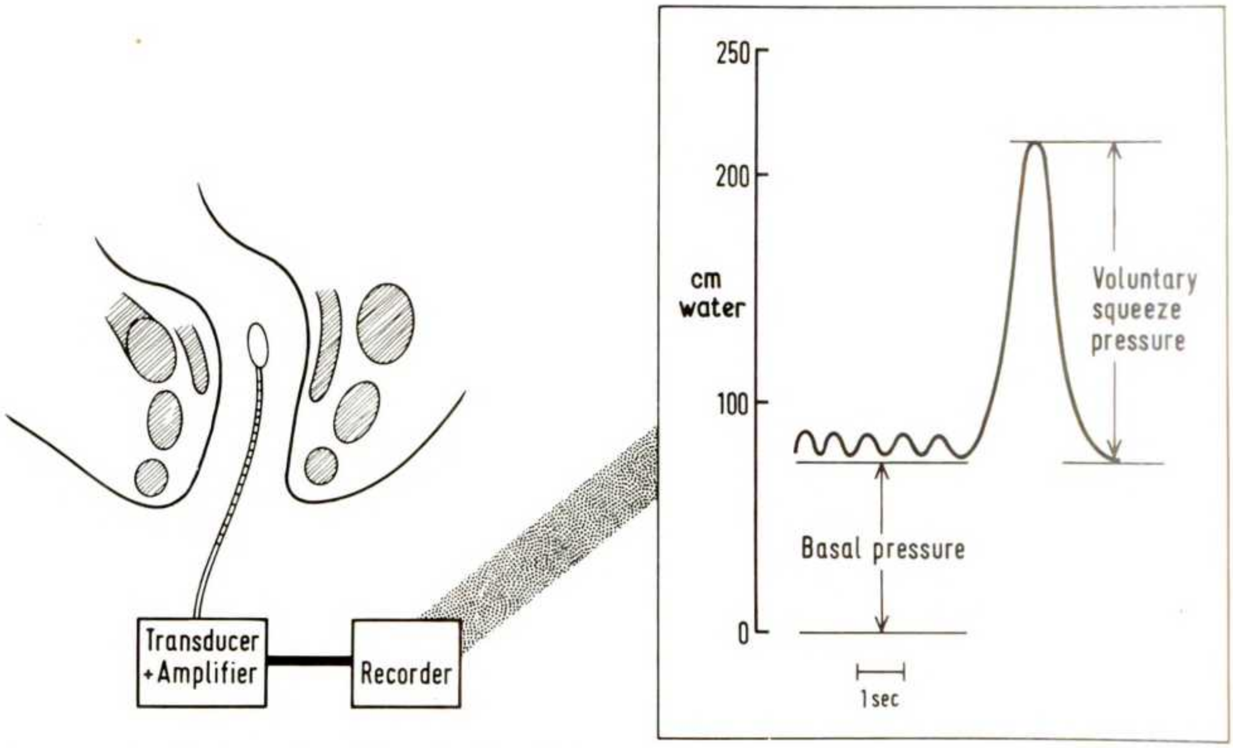

Figure 1 *The method of measuring the components of anal canal pressure*

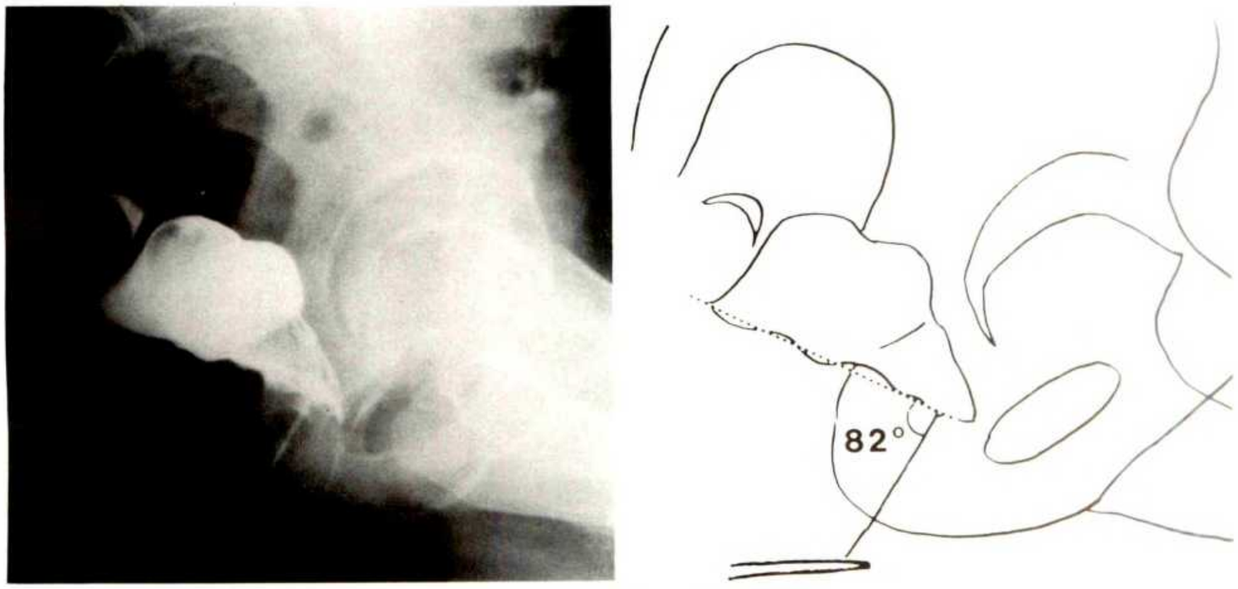

Figure 2 *Measurement of the anorectal angle from a lateral radiograph of the pelvis*

and designated the maximal basal and maximal voluntary squeeze pressures. A rise of 10 cm of water or more in the basal anal canal pressure was taken to indicate that the anal sphincter had been entered and, thereby, allowed its length to be measured from the pressure profile trace.

The minimum perceived and maximum tolerable volumes were measured as indices of rectal sensation, by inflation of a soft latex balloon within the rectum 10 cm from the anal verge.

The fibre density of the puborectalis muscle was measured as an index of reinnervation within the muscle. Use of a Medelec SF 37 single fibre EMG needle and standard EMG apparatus (MS6 and AA6 MkIII amplifier, Medelec) with spike triggering and delay line facilities (Neurolog NL200, NL202, Digitimer) allowed display and recording of individual motor unit potentials on UV sensitive paper (Linagraph Type 1895, Kodak). With the gain set at 200 μV/div and the filters at 500 Hz to 16 kHz, Stalberg's criteria[13] for eligible components (200 μV amplitude and a rise time of less than 300 μs) were used to calculate the fibre density from a minimum of 20 motor unit potentials recorded from both sides of the puborectalis. Such sampling required positioning of the electrode within the puborectalis muscle from at least four skin puncture sites. Confirmation that the needle was within the puborectalis was obtained by palpation with a finger in the anal canal.

Finally the anorectal angle was measured radiographically. An 8F Foley catheter was introduced into the rectum and its 3 ml balloon inflated. Gentle traction on the catheter lodged the balloon at the top of the anal canal; 20 ml of barium sulphate suspension was then introduced into the rectum through the catheter. There was occasionally some leakage of the barium suspension around the catheter as a result of a patulous anus in the incontinent patients but no difficulty was experienced with displacement of the catheter from the anus. With the hips flexed at 90° to the spine, lateral radiographs of the pelvis, centred on the anorectum, were taken at rest and during maximal straining efforts. The anorectal angle was measured from the radiograph (*Figure 2*) as the angle between the postero-inferior rectal wall and the anal canal as delineated by a column of barium within the catheter. The reproducibility of this measurement was investigated in eight subjects by repeating the study on two different days.

All patients were operated on by one consultant surgeon (N.S.W.).

They underwent the operation of postanal repair using the intersphincteric approach described by Parks[10]. After their exposure the ileococcygeal and pubococcygeal muscles were plicated with interrupted sutures (Vicryl, Ethicon Ltd., UK). The manometric and radiographic investigations were repeated 6 months after surgery and clinical assessment of the result was made after a median follow-up time of 26 months (range 15–48).

Statistical analysis

The results of these investigations were not normally distributed and have been quoted as median and range. Grouped data have been compared using the Mann–Whitney *U* test for unpaired data and the Wilcoxon rank sum test for paired data.

Results

The grading of the patients' incontinence before and after surgery is detailed in *Table 1*. Overall 14 (87·5 per cent) of the patients were improved by surgery with 6 (37·5 per cent) regaining normal continence. There were no specific intra-operative or postoperative difficulties to account for the unsatisfactory outcome in the two patients not improved by surgery.

Pre-operative electromyographic and paired pre- and postoperative manometric studies were available for all 16 patients and paired pre- and postoperative radiological studies were available for the last 12 patients investigated.

The puborectalis fibre density was significantly raised in the incontinent patients (median 1·75 (range 1·5–2·2); $P<0{\cdot}002$) compared with the control subjects (median 1·45 (range 1·4–1·7)).

The results of the other investigations are detailed in *Table 2*. Statistical analysis of the data for the incontinent patients as a whole and for those who had a successful outcome gave similar results. The data for the patients who remained incontinent was not analysed separately because of the small numbers involved. The basal and voluntary components of anal canal pressure and anal sphincter length were all significantly reduced pre-operatively in the incontinent patients compared with the control subjects. There was no significant change in the components of anal canal pressure after surgery and, despite a small but significant increase in sphincter length, none of these parameters were returned to normal by the operation.

Table 1 *The grades of incontinence before and after surgery*

	Grade of incontinence			
	A	B	C	D
Pre-operative	0	0	3	13
Postoperative	6	8	0	2

A, continent to solid and liquid stool and flatus; B, continent to solid and liquid stool but not to flatus; C, continent to solid but not to liquid stool or flatus; and D, incontinent to solid and liquid stool and flatus

Small increases in the minimum perceived and maximum tolerable volumes with surgery did not achieve statistical significance, but resulted in the maximum tolerable volume entering the normal range whilst the minimum perceived volume became abnormal when compared with the control subjects.

The pre-operative anorectal angle at rest (*Figure 3*) was significantly wider in the incontinent patients than in the control subjects, but it should be noted that five incontinent patients had anorectal angles within the normal range. The angle was not reduced by the operation, even in those patients with a successful outcome. Similarly the anorectal angle during straining (*Figure 4*) was not significantly reduced by postanal repair.

Repetition of anorectal angle measurements on two different days in eight patients gave a coefficient of correlation of 0·95 at rest and 0·9 during straining.

Discussion

The clinical results of this study confirm the findings of others[14-17] who have reported initial restoration of anal continence in approximately 80 per cent of patients by postanal repair. Parks[14] ascribed this benefit to increased efficiency of function of the voluntary anal sphincter muscles. If correct, such an effect would be expected to manifest itself as an increase in the voluntary component of the anal canal pressure and a reduction of the anorectal angle, both of which result from voluntary anal sphincter activity. In a subsequent paper Browning and Parks[15] described an increase in the voluntary component of anal canal pressure in patients with a successful outcome from postanal repair. Keighley and Fielding[16], however, reported that a successful outcome could be achieved without an increase in the voluntary component of anal canal pressure, a result confirmed by the present study. It would seem that an increase in the voluntary component of anal canal pressure is not necessary for restoration of continence.

Table 2 *Pre- and postoperative measurements of anal canal pressure, anorectal angle, rectal sensation and capacity, and sphinter length*

	All patients (*n* = 16)		Controls (*n* = 14)	Improved (*n* = 14)		Not improved (*n* = 2)	
	Pre-operative	Postoperative		Pre-operative	Postoperative	Pre-operative	Postoperative
Basal anal canal pressure (cmH_2O)	36** (10–85)	38** (12–105)	75 (50–126)	35** (10–85)	44** (12–105)	35 (32–38)	35 (30–40)
Voluntary anal canal pressure (cmH_2O)	51* (5–150)	32** (12–180)	94 (55–205)	43* (5–150)	32* (12–180)	73 (56–90)	51 (32–70)
Resting anorectal angle (degrees)	‡99·5** (90–112)	109·5** (79–118)	84 (75–94)	§96** (90–110)	107** (79–118)	111·6 (111–112)	111·5 (110–113)
Straining anorectal angle (degrees)	‡121·5* (94–137)	119* (79–138)	98 (80–114)	§121* (94–137)	119* (79–128)	128·5 (121–136)	126·5 (115–138)
Minimum perceived volume (ml)	51·5 (25–195)	65* (25–166)	35 (15–103)	53 (25–195)	65* (25–115)	35·5 (29–40)	105·5 (45–166)
Maximum tolerable volume (ml)	270* (150–500)	300 (130–450)	320 (270–420)	280* (150–500)	300 (130–450)	255 (250–260)	295 (250–340)
Sphincter length (cm)	2·0** (0–3·0)	2·5**† (0–3·5)	3.5 (3·0–4·0)	2·0** (0–3·0)	2·5**† (0–3·5)	2·0 (2·0–2·0)	2·25 (2·0–2·5)

Values are median and range. * Significantly different to controls $P<0{\cdot}05$; ** $P<0{\cdot}01$; † significantly different to pre-operative value, $P<0{\cdot}05$ (‡ $n=12$; § $n=10$)

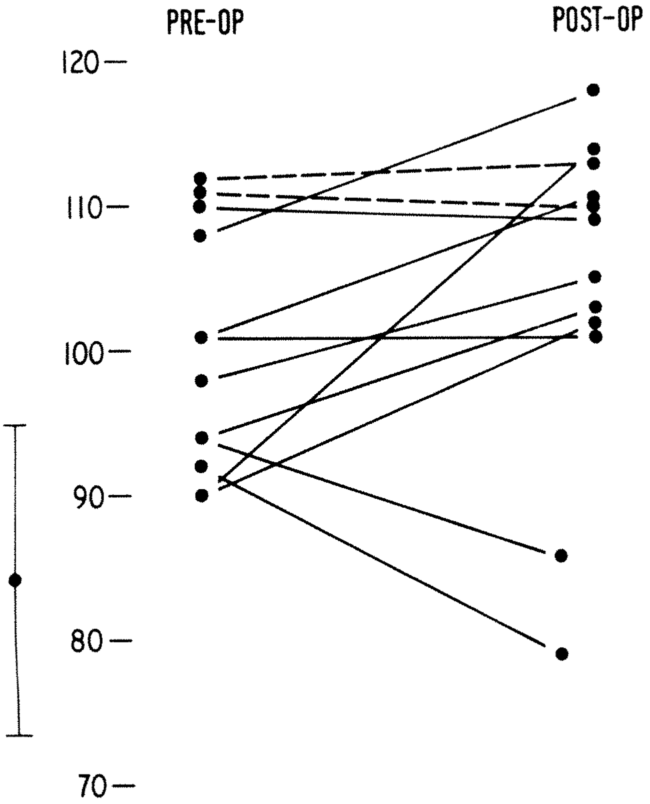

Figure 3 *The resting anorectal angle before and after postanal repair. Solid lines denote a successful outcome, broken lines an unsuccessful outcome. The normal range for the resting angle is shown to the left of the scale which is in degrees*

The early reports of the effects of postanal repair on the anorectal angle are somewhat anecdotal[3], the first detailed study being that of Preston *et al.*[18]. This study showed a reduction of the angle with surgery, but it may be criticized because the method used to measure the anorectal angle involved distension of the lower rectum and anal canal with a large barium-filled balloon. The authors state that many patients had difficulty retaining this balloon and this must have initiated varying degrees of voluntary and reflex activity in the pelvic floor muscles which may have biased the results. For the present study we used an orthodox method of measurement of the anorectal angle. We believed this method was unlikely to perturb the system since measurement was performed a short while after the introduction of the fine catheter and barium suspension into the rectum, when the subjects had become unaware of their presence. The day to day reproducibility of this method was also assessed and was found to be consistent.

The data with respect to the anorectal angle in our study are interesting for two reasons. Firstly, they demonstrate that a successful postanal repair does not depend on reduction of the anorectal angle, since the majority of patients improved by surgery had a wider anorectal angle after the operation. Secondly, five patients, all of whom were improved by surgery, had an anorectal angle within the normal range before the operation. This implies that the anorectal angle and, therefore, the flap valve theory, may not be as important for the maintenance of continence as has previously been stated. This view is supported by recent studies that have demonstrated widening of the anorectal angle by a similar degree in continent and incontinent patients with the descending perineum syndrome[4,5], and a study of the mechanism of continence that has failed to support the flap valve hypothesis[19].

Our study has shown that continence can be restored by postanal repair without improvement in either of the parameters attributable to the action of the voluntary anal sphincters. To what then may we attribute the improved continence after this operation? Previous authors[15,16] have reported significant increases in the basal anal canal pressure after postanal repair and Browning and Parks[15] reported an increase in the length of the resting high pressure zone in the anal canal. An increase in sphincter length was confirmed in the present study but the increase in basal anal canal pressures reported here did not reach statistical significance. It seems that the operation results in a pressure zone in the anal canal that is longer than that existing pre-operatively. It is believed that in health the basal anal canal pressure results from the activity of the involuntary internal anal sphincter[11,12], providing the measuring probe has a small diameter (< 7 mm). Whether basal anal canal pressure represents internal sphincter activity after surgery is unknown. It is possible that a component of the resting anal canal pressure recorded after postanal repair accrued from passive stretching, by the probe, of fibrous tissue induced by surgery. Similarly the pubococcygeus/puborectalis parts of the pelvic floor may be 'stiffened' by fibrosis resulting in decreased deformability and consequently increased passive resistance of the rectal outlet.

The other factors measured in this study, rectal sensation and capacity, showed no significant change with operation and were unlikely to have contributed to the benefit obtained from surgery.

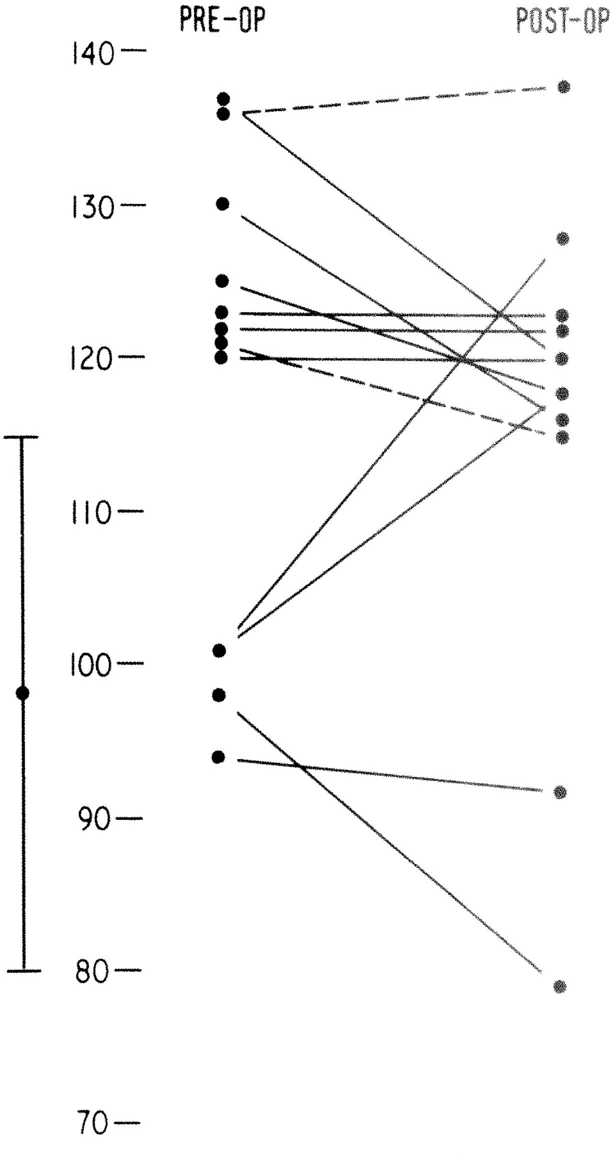

Figure 4 *The anorectal angle during straining before and after postanal repair. Key as for* Figure 3

The aim of this study was to identify the factors responsible for a successful outcome from the operation of postanal repair, and thereby aid selection of patients for the operation. We have shown that improvement of function after this operation does not seem to be related to increased efficiency of the voluntary sphincter muscles, or to changes in rectal sensation or capacity. Lengthening of the anal canal high pressure zone may contribute to a successful result. From a practical point of view, perhaps the most important finding was that a significant number of incontinent patients have an anorectal angle within the normal range and yet such individuals may have continence restored by a postanal repair. Hence it follows that a wide anorectal angle should not be used as a criterion for surgery, and it would appear that all patients with neurogenic faecal incontinence, who have severe symptoms and who are fit for surgery, should be offered the operation of postanal repair.

Acknowledgements

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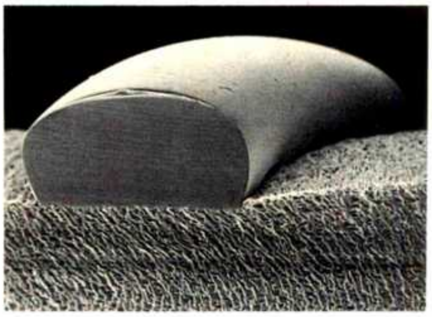

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Investigation of anorectal function

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Anorectal function tests were performed in 280 consecutive patients, who were referred for evaluation of different anorectal disorders. The relationship between the estimated anal sphincter pressure on digital palpation and the measured pressure on anal manometry was investigated and the interrelationship between anal manometry, rectal capacity and the saline infusion test was defined. A significant correlation ($P<0{\cdot}001$) *was found between digitally and manometrically measured anal sphincter pressure. Considering the relationship between the three specific anorectal function tests, only manometry and the saline infusion test correlated to some extent* ($P<0{\cdot}01$). *This study shows that digital palpation is helpful in anorectal function investigation, but to establish the exact anal pressures, anal manometry is mandatory. Furthermore, the poor correlation observed indicates that single tests represent different aspects of anorectal function and therefore they need to be performed together.*

Keywords: Anal manometry, rectal capacity, incontinence

Anorectal function tests are commonly performed in patients with anorectal disorders. Few authors have studied the relationship between the different tests[1,2]. Therefore in 280 patients, referred for evaluation of anorectal disorders, we studied the relationship between the anal sphincter pressure estimated by digital palpation and the anal sphincter pressure measured by manometry, as well as the correlations between the results of anal manometry, the saline infusion test and measurement of rectal capacity.

Patients and methods

Between August 1981 and October 1985, 280 patients (117 men and 163 women, age 6–86 years, mean 50 years) were referred for investigation of anorectal function for different reasons (incontinence, soiling, constipation, fissure, fistulae, haemorrhoids, proctitis). All clinical and anorectal investigations were performed by two investigators, experienced in this field (R.F B. and E.K.K) A detailed medical history was taken.

Anal presure measurement

The anal sphincter pressures (maximal basal pressure = MBP and maximal squeeze pressure = MSP) were first estimated by digital palpation and scored as weak, moderate, normal or increased, corresponding with the expected MBP pressure of 0–20, 20–40, 40–80 and >80 mmHg and MSP 0–20, 20–60, 60–160 and >160 mmHg respectively Anal manometry was performed with the patients in the left lateral position. To avoid sphincter irritation no enema was given. A water-filled open-tipped catheter 'low compliance' perfusion system with pressure transducers (Beckman type 4-527-C) connected to a dynograph recorder (Beckman R 611) was introduced. A five-lumen polyvinyl rectal catheter with an internal diameter of 1·1 mm was used Four side ports were situated 0·5 mm apart in a longitudinal axis and 60 degrees apart around the circumference of the probe The perfusion rate was 0·5 ml/min. The fifth channel was connected with the rectal balloon at the tip and could be insufflated with a syringe. After positioning the catheter was left to accommodate for several minutes and the rectal pressure was set to zero. The catheter was then withdrawn at steps of 1 cm and remained for at least 2 minutes at each station in the anal canal MBP (normal value 40–80 mmHg, references 1–5) was noted as the highest recording in any of the four leads The catheter was then introduced and withdrawn again in 1 cm steps, while the patient was asked to squeeze twice at each station to register the MSP (normal value $\geqslant +60$ mmHg, references 1–5), from which was calculated the maximum increase in pressure.

Saline infusion test

This is a test for fluid incontinence and was performed according to the method of Read *et al.*[1]: 1500 ml of isotonic saline at body temperature was infused into the rectum at a rate of 60 ml/min. The time of the first leak (TFL) and the total volume leaked (TVL) were noted.

Rectal capacity

The rectal capacity was measured by inflating a balloon catheter in the rectum by slow increments of 10 ml until the maximum tolerated volume was reached.

Statistical analysis was performed with the Pearson product-moment correlation coefficient and the Spearman rank correlation coefficient. All results are expressed as mean ±s.d.

Results

Results of the individual tests are listed in *Table 1*. The MBP for men was 71 ± 30 mmHg and for women it was 56 ± 24 mmHg. The MSP for men was 130 ± 67 mmHg and for women it was 70 ± 48 mmHg. Women appeared to leak earlier and with larger volumes than men ($P<0{\cdot}01$).

Relationship between digital palpation and anal manometry

The correlation coefficient between digital palpation at rest and MBP was 0·56 ($P<0{\cdot}001$) (*Figure 1*) and between digital palpation during squeeze and MSP 0·76 ($P<0{\cdot}001$) (*Figure 2*) In our population 64 per cent had a normal MBP. The sensitivity of digital palpation in estimating a normal MBP was 72 per cent and the specificity 67 per cent. The positive predictive value was 69 per cent, the negative predictive value 60 per cent. A normal MSP was found in 70 per cent of our patients. The sensitivity of digital palpation in estimating a normal MSP was 72 per cent, the specificity 97 per cent with a positive predictive value of 98 per cent and a negative predictive value of 60 per cent.

Correlations between the tests

The correlation coefficient between MBP and MSP was 0·38 ($P<0{\cdot}001$) and between TFL and TVL it was $-0{\cdot}80$ ($P<0{\cdot}001$; *Table 2*). *Table 3* shows the correlation coefficients between anal manometry, saline infusion test and rectal capacity with significant values ($P<0{\cdot}01$) for the correlation between the anal manometry and the saline infusion test. The rectal capacity did not correlate with the other two tests.

Discussion

Anal continence depends on the integration of the anal sphincters, the anorectal angle formed by the puborectalis

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Table 1 *Results of anal manometry, saline infusion test and rectal capacity*

Anal manometry	*n*	Mean±s.d.	Range			
MBP (mmHg)						
All	280	62±27	0–140			
Men	117	71±30	0–140			
Women	163	56±24	10–120			
MSP (mmHg)						
All	275	96±64	0–300			
Men	116	130±67	0–300			
Women	159	70±48	0–260			
Saline infusion test TFL (min)	*n*	<5	5–10	10–20	>20	None
All	183	84	31	26	8	34
Men	69	22	16	12	1	18
Women	114	62	15	14	7	16
TVL (ml)	*n*	<10	10–100	100–500	500–1000	>1000
All	181	38	8	19	34	82
Men	68	21	3	6	15	23
Women	113	17	5	13	19	59
Rectal capacity (ml)	*n*	<200	200–400	>400		
All	93	28	52	13		
Men	40	14	21	5		
Women	53	14	31	8		

MBP, maximal basal pressure; MSP, maximal squeeze pressure; TFL, time of first leak; TVL, total volume leaked

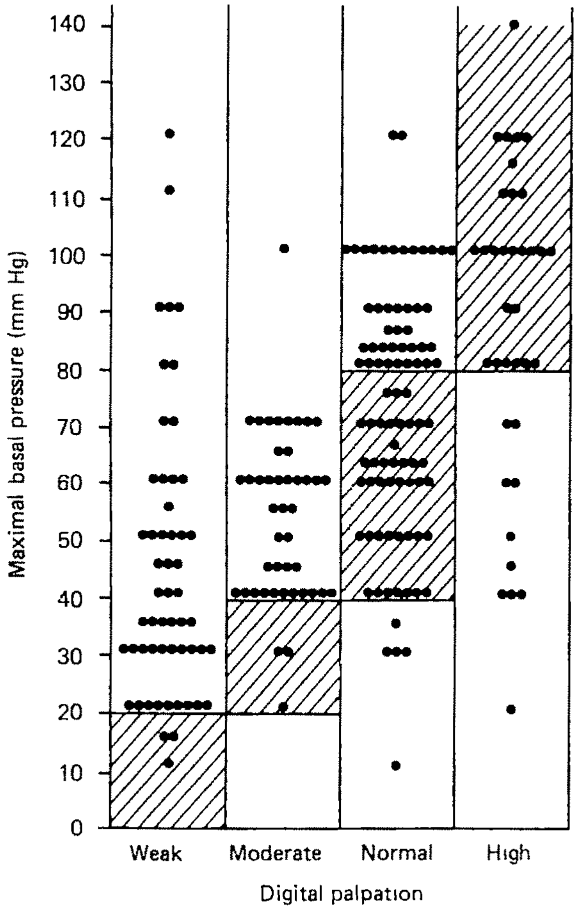

Figure 1 *Maximal basal pressure: relationship between digital palpation and anal manometry.* ▨*, expected value,* ●*, actual value of each patient*

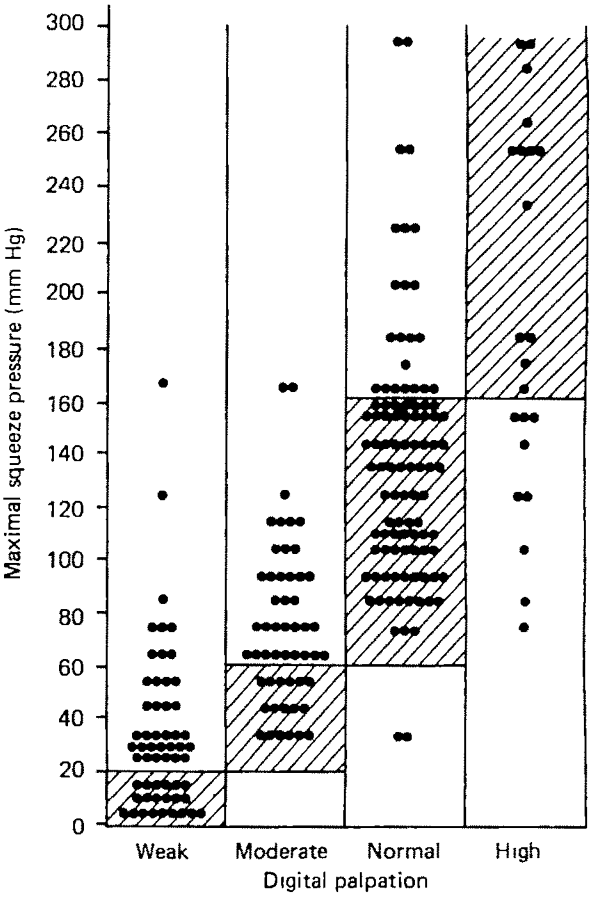

Figure 2 *Maximal squeeze pressure. relationship between digital palpation and anal manometry.* ▨*, expected value;* ●*, actual value of each patient*

Table 2 *Saline infusion test: relationship between time of first leak and total volume leaked*

Time to first leak (min)	Total volume leaked (ml)				
	<10	10–100	100–500	500–1000	>1000
<5	1	1	5	12	64
5–10	2	2	3	11	13
10–20	1	2	7	10	5
>20	—	3	4	1	—
None	34	—	—	—	—

Spearman rank correlation coefficient: −0·80 ($P<0·001$); $n=181$

Table 3 *Correlation coefficients between anal manometry, saline infusion test and rectal capacity*

	Saline infusion test		Rectal capacity
	Time 1st leak	Total volume leaked	
Rectal capacity	0·27	−0·31	***
Anal manometry:			
MBP	0·39†	−0·34†	0·18
MSP	0·47†	−0·45†	−0·16

Spearman rank correlation coefficient († $P<0·01$). MBP, maximal basal pressure; MSP, maximal squeeze pressure

muscle of the pelvic floor[6], the rectal capacity or compliance[7], and the consistency of the stools. The exact role of sensory awareness has yet to be established[8,9]. Anal manometry is being used to measure objectively the anal sphincter pressures. In contrast to Read *et al.*[1] and Matheson and Keighley[2] we found, using the same methods, a significant correlation for the whole group between the digitally estimated anal sphincter pressure and the pressure measured with anal manometry. However, neither the sensitivity nor the specificity of digital palpation in estimating normal sphincter pressures is very high and because the predictive value of digital palpation is low, anal manometry is obligatory to establish exact anal sphincter pressures, especially in therapeutic (medical or surgical) evaluation. The resting tone of the internal anal sphincter contributes 85 per cent and the resting tone of the external anal sphincter 15 per cent to the MBP in normal persons[10], while the MSP is a consequence of the external anal sphincter contraction. A low correlation was found between MBP and MSP. This may suggest that the internal and external sphincter are largely independent variables in spite of their close anatomical and functional relationship. The difference in innervation (autonomic innervation *versus* spinal innervation) offers an explanation.

The saline infusion test measures incontinence for fluids[1]. The good correlation between the TFL and TVL in our patients confirms the results obtained in the original study[1]. In our experience the test has to be performed for the full 25 minutes because there are patients who continuously leak small amounts and patients who have just one major leak near the end of the test period. The saline infusion test showed only a low correlation with the MBP. This suggests that a low basal tone of the anal sphincter alone hardly influences continence. Between the MSP and the saline infusion test a significant but moderate correlation of 0·56 was found, demonstrating that an impaired external sphincter does not always lead to incontinence or that good sphincter tone cannot always prevent it. In our study the rectal capacity neither correlated with the results of anal manometry nor with those of the saline infusion test. This implies that a small capacity does not automatically lead to incontinence or that a large rectal capacity can prevent incontinence. It also seems that a small rectal capacity from whatever cause may not affect sphincter pressure. However, in patients with chronic radiation injury there is internal sphincter dysfunction[11]. In addition, few patients with Crohn's disease[7] or ulcerative colitis[12] were found to be incontinent despite small rectal capacities.

We conclude that digital palpation is only an approximate method of measuring the anal sphincter pressures and that additional anal manometry is warranted, especially in situations where therapeutic intervention such as surgery or biofeedback is considered. Analysis of the three anorectal function tests shows that between these tests there is only a poor correlation or no correlation at all, demonstrating that these tests measure different aspects of the anorectal function. Therefore to obtain a complete functional analysis, these tests have to be performed together.

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Anal fissure in Crohn's disease

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There is little information on the natural history of anal fissure in Crohn's disease. The case notes of all new patients with Crohn's disease attending one hospital between 1977 and 1983 were reviewed: there were 61 patients with this diagnosis and an unhealed anal fissure as the only anal lesion. Of these 61 patients the fissure healed in 42 (69 per cent) during medical treatment of the intestinal disease. Ten patients (16 per cent) developed other anal lesions and in the remaining nine patients the fissure remained unhealed at the time of rectal excision (six) or last out-patient attendance (three). Activity of the fissure did not reflect disease activity elsewhere in 11 cases in whom healing of the fissure occurred despite progressive intestinal disease subsequently requiring resection. This study validates the policy of conservative management of anal fissure in Crohn's disease with anal surgery (required in 9·8 per cent of patients in this series) being reserved for the development of other anal disease.

Keywords: Crohn's disease, anal fissure

Most clinicians follow a conservative policy in the treatment of fissure when associated with Crohn's disease. There is at present only one study in the literature relating to the subject: in this, 53 patients with an anal fissure were reviewed at 10 years; the fissure was still present in 10 (19 per cent) but little further information was given[1]. Anecdotal accounts abound but neither the fate of the patient nor of the fissure is known, nor whether conservative treatment is appropriate. In this study we have attempted to provide that information.

Patients and methods

Sixty-one new patients with Crohn's disease and no previous bowel surgery, who had an unhealed anal fissure as the only anal lesion when presenting to St. Mark's Hospital between 1977 and 1983, were identified and their case notes were reviewed retrospectively. These 61 patients formed 26 per cent of 233 new patients with Crohn's disease and no previous bowel resection seen during this period. The diagnosis of fissure, as distinct from an anal ulcer, was established by consultants in all patients and the follow-up was by regular clinical assessment at out-patient attendances.

Results

There were 38 women (mean age 28·5±14·2 years) and 23 men (mean age 28·3±13·8 years). The mean follow-up was 58·8 months (range 2–114 months). There was small and large bowel involvement in 28, large bowel only in 26 and small bowel only in 4 patients; extensive disease including the upper gastrointestinal tract was present in 3 patients. Forty-one patients (67 per cent) had a single fissure and twenty (33 per cent) had multiple fissures with the distribution shown in *Figure 1*. In only six patients was the fissure situated away from the midline. In 54 patients with adequate documentation, pain was present in 24 (44 per cent).

Treatment and outcome (Table 1)

All patients had medical treatment for the intestinal disease and none had any local treatment for the fissure except for anaesthetic jelly in some patients with pain.

Medical treatment only. In 24 patients having systemic medical treatment only, the fissure healed in 19 although in 3 there was a period of relapse. Of the remaining five, three developed other anal lesions and two were unhealed when lost to follow-up at 7 and 54 months respectively. The mean follow-up in this group was 49·4 months and the mean time to healing was 8·4 months.

Medical treatment and anal surgery. Six patients had an anal procedure as the only surgery in addition to medical treatment but in no case was this a definitive fissure operation. In three an examination under anaesthetic was carried out and in three an abscess or fistula was treated. In two of the patients

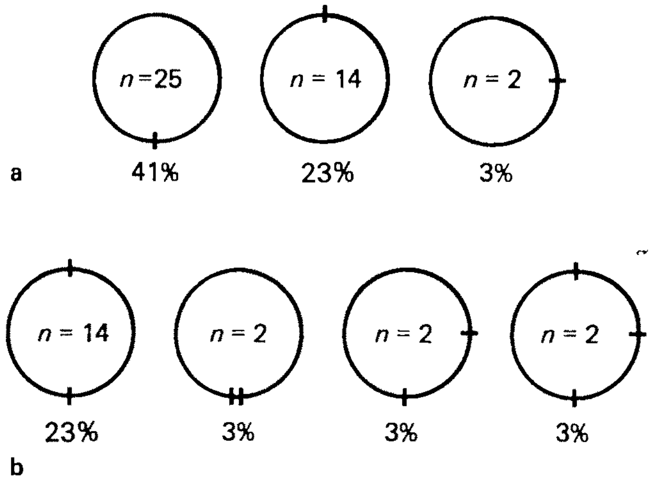

Figure 1 *Position of the fissure in* **a**, *41 patients with a single site and* **b**, *20 patients with multiple sites. Values are percentages of the total number of patients (61); n = the number of patients*

Table 1 *Overall outcome of systemic medical treatment in 61 patients with Crohn's disease and an anal fissure*

	Medical treatment of intestinal disease only (24 patients)	Anal surgery only (6 patients)	Later resection of intestinal disease (31 patients)
Healing	19	2	21
Other anal lesion	3	4	3
Unhealed	2		7

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examined under anaesthetic the fissure healed after the procedure while the other developed a fistula some months later.

Later intestinal surgery. Thirty-one patients required abdominal surgery for resection of intestinal disease and seven of these had an anal procedure in addition. In only one case was the anal operation a definitive operation for fissure, namely a lateral anal sphincterotomy. This patient developed an abscess and fistula at the site of the sphincterotomy and ultimately required excision of the rectum for this complication. The other patients had an examination under anaesthetic (two patients) or drainage of abscess (four patients).

Of the 31 patients, 19 had sustained healing of the fissure, pre-operatively in 11 and postoperatively in 8 (all within 3 months of surgery). In four patients the fissure healed but relapsed later: in two further healing took place, one developed another anal lesion and one remained unhealed 84 months after the intestinal resection. In the 13 patients requiring rectal excision, the fissure had healed pre-operatively in 5, was unhealed in 6, and 2 patients had developed an anal fistula.

There was no difference in healing between single and multiple fissures or between painful or painless fissures, and healing was unrelated to the site of bowel involvement.

Overall, healing of the fissure without any local surgical treatment occurred in 42 patients (69 per cent) although in 5 there was a period of relapse. Ten patients progressed to develop other anal lesions which subsequently dominated the anal pathology and required local surgery in six. In the remaining nine patients the fissure was either unhealed at rectal excision (six patients), unhealed when lost to follow-up (two patients) or unhealed despite resection of abdominal disease (one patient).

Discussion

Although the mean healing time was long (6·5 months), overall 49 per cent (30 out of 61) patients exhibited primary sustained healing of the fissure during medical treatment for their intestinal disease. Although this might seem to support the view that fissure is a reflection of the activity of intestinal disease, this is probably not the case as 11 of these patients subsequently required resection for progressive intra-abdominal disease. However, in the eight with healing of the fissure after surgical resection this occurred rapidly (all within 3 months) and thus in some patients (but not all) healing of a fissure may reflect disease activity elsewhere.

Some authors suggest that fissures in Crohn's disease occur more commonly in the lateral quadrants, i.e. away from the midline[2,3]. However, this study supports the view of Hughes[4] that the majority are located in the anterior and/or posterior quadrants.

In contrast to idiopathic anal fissure which is usually painful, fissure in Crohn's disease is usually considered to be painless[1-7]; however, in these patients 45 per cent had associated pain not attributable to local sepsis. This highlights the fact that painful fissures can and do occur in Crohn's disease, and the suspicion of Crohn's disease should not be lessened because of the presence of pain.

The healing and benign course of the anal fissure in the majority of these patients reaffirms the view of Hughes[4], Buchmann *et al.*[1] and Goligher[3] that the majority of these fissures should be treated conservatively. Anal surgery should be reserved for the development of other complications which can be expected to occur in about 10 per cent of patients. In patients with persistent pain it would be prudent to perform a careful examination under anaesthetic to exclude sepsis and it may be that the mild dilatation associated with this will be sufficient to promote healing (as occurred in two patients in this series) and produce the same effect as the cautious sphincter stretch advocated by Goligher in these exceptional cases[3]. The unfavourable outcome in the only patient having a lateral anal sphincterotomy suggests extreme caution in following the advice of Sohn and Korelitz[5] in performing a lateral anal sphincterotomy in patients who have pain and fail to respond to medical therapy.

In summary, as in idiopathic anal fissure, the majority of fissures occur in the anterior and posterior quadrants or a combination of both. Contrary to general opinion, fissure associated with Crohn's disease is often painful and the presence of pain should not lessen the clinical suspicion of Crohn's disease. The healing of a fissure can occur despite progressive abdominal disease but with resection of abdominal disease rapid healing can usually be expected. Anal surgery for a fissure associated with Crohn's disease is indicated rarely but may be necessary if other anal manifestations develop.

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Appendicitis and schistosomiasis

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A retrospective clinical and pathological study of 15 cases associated with schistosomiasis drawn from 1920 patients undergoing appendicectomy is discussed. The average age of the patients was 31·6 years with a 12:3 male predominance. Hepatomegaly, past or present jaundice, or splenomegaly were not observed. One patient had a previous history of similar right lower quadrant pain for several days. Eighty per cent of the cases showed an inflammatory reaction on pathological examination. In the remaining 20 per cent no inflammation was seen, but there was severe congestion mainly involving the subserosal blood vessels. Schistosoma haematobium *was present in 80 per cent of the cases.*

Keywords: Appendix, tropical, schistosomiasis

Acute appendicitis is the most frequent acute surgical condition affecting the abdomen. It represents between 20 and 30 per cent of all surgical procedures carried out at the Riyadh Central Hospital and Sulaimania Surgical Center, Riyadh, Saudi Arabia. It is more common in men in the second and third decades of life, and obstruction of the appendiceal lumen is considered to be one of the major aetiological factors.

Schistosomiasis, a water-borne trematode infection, is one of the most widespread parasitic diseases in the world and 300×10^6 people are probably affected[1,2]. It occurs frequently in Saudi Arabia[3] and has been observed in the Riyadh population[4]. To study the association of appendicitis with schistosomiasis in the appendix, a detailed study was carried out at the Sulaimania Surgical Center of Riyadh, a branch of the Riyadh Central Hospital.

Patients and methods

A total of 3800 patients were admitted between September 1984 and September 1986 to the surgical services mentioned above with a diagnosis of acute appendicitis; 3230 patients underwent appendicectomy and their histopathological reports showed that 63 (2 per cent) were associated with *Schistosoma* ova in the appendix.

A protocol to study schistosomiasis and acute appendicitis was then established. In the 10-month period between November 1985 and September 1986, 1920 such patients were operated on and 15 patients were found to have *Schistosoma* associated with appendicitis. A careful clinical history of these 15 patients was obtained with emphasis on previous similar abdominal attacks. The presence of jaundice, hepatomegaly or splenomegaly was ascertained and routine haematological measurements, urinalysis and faecal examination was undertaken.

Three sections of the appendix were taken for pathological examination. A routine haematoxylin and eosin stain of the slides and an acid-fast stain to distinguish *Schistosoma haematobium* (acid-fast negative ova shell) from *S. mansoni* and *S. japonicum* (acid-fast positive ova shell) were performed[5].

Results

There were twelve males and three females and the average age was 31·6 years. Eleven patients were Egyptian, three were Yemeni and one Saudi. All of the patients had a clinical history of right iliac fossa pain with rebound tendency. Jaundice, hepatomegaly or splenomegaly were not found. Three of them had fever. One patient had a history of similar episodes on two or three occasions 1–2 months earlier. None of the patients had a history of haematuria or dysuria. Pathological reports showed that 12 of the 15 cases were associated with inflammatory changes in the appendix; acute inflammatory changes were present in nine of the cases and acute and chronic inflammatory changes with granulomatous and fibrotic reaction were present in three. *Schistosoma haematobium* was involved in 12 of the 15 cases. Two of three cases with *Schistosoma mansoni* infestation had a positive stool examination. Histopathological study in these two cases revealed positive acid-fast egg shells in the appendix (*Figure 1*).

No ova of *Schistosoma* were found in the urine despite the high frequency of the *Schistosoma haematobium* ova found in the appendix. In six of the cases with acute appendicitis, severe 'embolization' and ova impaction were present in the vascular lumen and in some instances they were associated with haemorrhagic necrosis, indicating a direct participation in the pathology of the acute appendicitis.

One case of mixed infestation with *S. haematobium* and *S. mansoni* was observed.

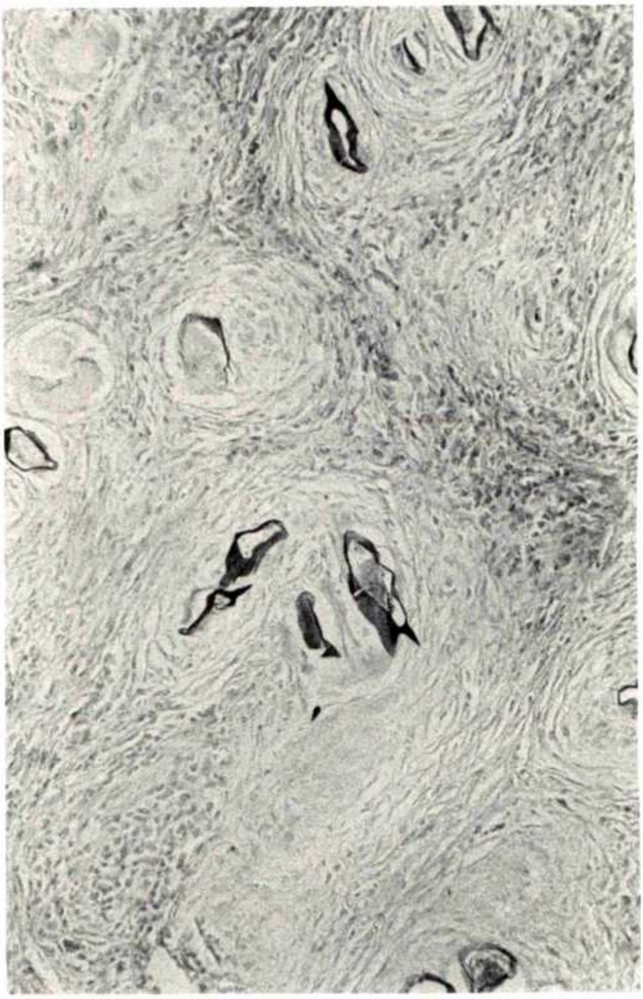

Figure 1 *Granulomatous reaction around eggs of* Schistosoma mansoni *easily identified by acid-fast positive reaction of the shells. Magnification × 400*

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Discussion

Of our 15 patients with acute appendicitis in association with schistosomiasis, none had hepatosplenomegaly or a present or past history of jaundice. Dysuria suggestive of chronic infection was present in only one case who had a history of similar abdominal pain in the lower abdominal quadrant. The three cases with fever did not show hepatomegaly, splenomegaly, urticaria or eosinophilia, changes often associated with acute infection[6-8].

In 60 per cent of our cases of acute appendicitis the number of eggs or the granulomatous reaction did not appear sufficiently severe to be the primary cause of the inflammatory process. However, it may be an important contributor to inflammation through congestion, oedema and subsequent obstruction of the appendiceal lumen with stagnation and an overgrowth of pathogenic bacteria. The pathological finding in our study suggests that the number of deposited eggs in the superior mesenteric vein and particularly in the appendiceal vein may be related to the degree of inflammation. If the number is small, acute congestion with minimal luminal obstruction and marked serosal distension will occur which could explain the symptoms and signs of acute pain in the lower quadrant. If deposition is severe, impaction of the eggs in the lumen of capillaries will produce ischaemic changes with severe congestion, haemorrhage, necrosis, mucosal ulceration and further penetration of the bacteria in the appendiceal wall with the more extensive inflammatory reaction observed in acute appendicitis.

An interesting but unexplained finding was the absence of *Schistosoma* eggs in the urine despite the fact that 80 per cent of the cases of appendicitis were associated with the presence of *S. haematobium*. This association merits further investigation to determine whether it reflects the frequency of species found in an infested area.

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Prognosis after simple incision and drainage for a first-episode acute pilonidal abscess

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During a 3-year period 73 patients were treated consecutively for a first-episode acute pilonidal abscess with simple incision and drainage under local anaesthesia. In all cases the treatment relieved symptoms and all patients returned to work immediately after treatment. Healing per primam *occurred in 42 patients (58 per cent; 95 per cent confidence limits: 45–69) within 10 weeks after treatment. These patients had significantly fewer pits and lateral tracts compared with patients who developed excessive granulation tissue after incision and who required definitive surgical treatment later. Nine patients (21 per cent; 95 per cent confidence limits: 10–37) with healing* per primam *developed recurrence of their pilonidal disease during the prospective follow-up period (median follow-up period was 60 months, range 36–84 months). Actuarial analysis of the data revealed a constant cure rate of 76 per cent (95 per cent confidence limits: 57–95) after 18 months.*

Keywords: Pilonidal abscess, simple incision, cure rate, recurrence rate

Simple incision and drainage of a pilonidal abscess is preferred over definitive treatment, because of infection and marked hyperaemia of adjacent tissues. Definitive treatment of the chronic pilonidal sinus is recommended 4–8 weeks after incision and drainage[1,2]. However, it is not known how often healing *per primam* can be expected after simple incision and drainage, thereby avoiding definitive treatment.

The present prospective study deals with the results of simple incision and drainage for a first-episode acute pilonidal abscess with special emphasis on cure rate and recurrence rate among patients with healing *per primam* in a follow-up study of consecutively treated patients.

Patients and methods

Patients

During the period January 1980–December 1983, 46 men and 27 women, median age 20 years (range 16–29 years) were treated for a first-episode pilonidal abscess in one of the following out-patient clinics: General Practice and Surgical Clinic, Lægehuset, Rønnebær Allé, Elsinore, Denmark. The median duration of symptoms before treatment was 8 days (range 5–11 days).

Operative treatment

With the patient in the prone position, 1·0 per cent lignocaine with 1:200000 epinephrine solution was injected with a fine needle into the skin overlying the fluctuant area. No patient received sedation before operation. After carefully shaving the area, a cruciform incision was made over the most fluctuant or tender area. The four corners of the cruciform incision were excised to allow adequate drainage. There was no curettage of the wound. Haemostasis was achieved by light gauze packing. A small dressing was applied. The patients were told to take a daily hot shower and to abrade the wound with a wash cloth.

The patients were examined every 2 weeks until complete healing *per primam*, or for 12 weeks. At each visit the area around the wound was carefully shaved. The need for definitive surgery was ascertained at the 12-week visit. Patients with unhealed wounds were treated by Lord and Millar's brush technique[3,4].

Follow-up

Patients with wounds healed *per primam* were followed clinically every 6 months. No patients were lost to follow-up. The median follow-up period was 60 months (range 36–84 months).

Data analysis

Recurrence risk and cure rate were analysed by an actuarial method for small patient series with different lengths of observation[5]. Results are given as percentage cure with 95 per cent confidence limits.

Results

All abscesses could be drained adequately under local anaesthesia and the treatment resulted in prompt relief of pain and discomfort. Median number of days of work was two (range 0–7 days). Of 73 patients, 42 healed *per primam*, 57·5 per cent; 45–69), whereas 31 (42·5 per cent; 31·0–54·6) suffered from excessive granulation tissue 12 weeks after incision and drainage of the abscess and underwent definitive treatment. No increase in cure rate was found after 10 weeks. The median number of weeks before healing *per primam* was 5 weeks (range 3–10 weeks). Nine patients (21·4 per cent; 10·3–36·8) with healing *per primam* had a recurrence during the observation period and developed a chronic pilonidal sinus, the latest recurrence being diagnosed 18 months after healing *per primam*. Actuarial analysis of the results is shown in *Figure 1*. According to this analysis, the overall cure rate after 60 months was 76 per cent (95 per cent confidence limits: 57–95).

Table 1 demonstrates that patients with healing *per primam* had significantly fewer pits ($P < 0{\cdot}01$) and lateral tracts ($P < 0{\cdot}05$) compared with patients with unhealed lesions after simple incision and drainage.

Discussion

The present prospective study has shown that simple incision and drainage of a first-episode pilonidal abscess cures 58 per cent of patients within 10 weeks of treatment. Primarily cured patients had significantly fewer pits and lateral tracts compared with patients with unhealed lesions. The recurrence rate of pilonidal disease after primary healing was 21 per cent. The estimated cure rate among these patients followed a declining course during the first 18 months of observation; thereafter, the curve labelled off in about 76 per cent and remained constant during the observation period.

Virtues of the procedure are that it causes a minimal degree of surgical trauma and can be performed easily under local

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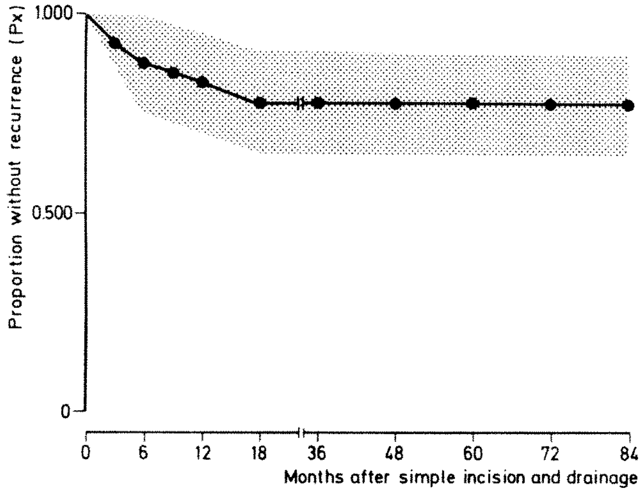

Figure 2 *Cure rates after treatment of patients with a first-episode acute pilonidal abscess by simple incision and drainage.* ▨, *95 per cent confidence limits*

anaesthesia as an out-patient procedure. The procedure causes a dramatic relief of symptoms and all patients may return to work within a few days. The advantage of the procedure is, furthermore, that it is not only a palliative but also a curative procedure for pilonidal disease in about 60 per cent of the cases. The recurrence and cure rates observed among these patients are not different from those reported for electively treated patients who have undergone more extensive surgical procedures[6,7].

This study demonstrates that it can take up to 10 weeks for an incised pilonidal sinus to heal *per primam*. Thus, the decision to offer definitive treatment should not be taken earlier. The study leaves the unanswered question of why some pilonidal abscesses heal after incision. Our study suggests that this is related to the extent of the pilonidal sinus, as patients with several pits and lateral tracts required definitive treatment more frequently than patients with none or only a few of these characteristics. Therefore, if patients with acute pilonidal abscesses are carefully examined with respect to the presence of pits and lateral tracts, it should be possible to select some patients and treat them initially with more definitive procedures such as Lord and Millar's brush technique.

Table 1 *Healing* per primam *in relation to number of pits, midline, and lateral tracts in patients with acute pilonidal abscesses treated by simple incision and drainage*

	Healing *per primam* ($n = 42$)	Unhealed ($n = 31$)	Level of significance
No. of pits	89	133	$P < 0{\cdot}01$
No. of midline tracts	29	28	n.s.
No. of lateral tracts	51	77	$P < 0{\cdot}05$

n.s., not significant

The observed recurrence rate of 21 per cent among patients initially cured by simple incision does not differ from the results obtained with more extensive surgical procedures.

In conclusion, simple incision and drainage is the treatment of choice. It is easily performed under local anaesthesia in the office and offers the patients immediate relief of pain and discomfort without hospitalization.

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Treatment of 'inoperable' neck nodes using surgical clearance and postoperative interstitial irradiation

The inability to remove all disease at the time of a radical neck dissection, or inoperable recurrent disease after a neck dissection, are both familiar problems for the head and neck surgeon. All too frequently the conventional treatment options have already been used, the patient having received external beam radiotherapy and possibly cytotoxic chemotherapy. In such circumstances, and provided that the primary tumour remains under control, a positive approach to the further management of the neck metastases should be adopted, given that the patient is in otherwise reasonable health and does not have gross distant metastatic disease. We describe our experience with postoperative interstitial irradiation (brachytherapy) using after-loaded iridium-192 (^{192}Ir) wires positioned at the site of the tumour after its surgical exposure and debulking or clearance. All the treated patients had previously received external beam irradiation to the neck and in the first three cases local skin necrosis occurred as a sequel to interstitial implantation. Therefore, in the other five patients, cutaneous or myocutaneous flaps were used to resurface the area at the time of implant placement. This combination of technqiues, which has not been described previously, provided local tumour control in four out of the five cases without irradiation necrosis occurring in any of them.

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Keywords: Interstitial irradiation, resurfacing, inoperable cervical nodes

Crile's development of the radical neck dissection over 80 years ago[1] was based on the observation that primary squamous cell carcinomas in the head and neck region metastasize principally to the cervical lymph nodes. The nodes appear to hold the disease regionally for a considerable period of time before more distant dissemination occurs. It has been shown that a radical neck dissection performed appropriately for involved lymph nodes can result in the cure of the patient[2], and the operation has long been a keystone in the surgical management of head and neck malignancy. However, there remain two groups of patients for whom a radical neck dissection is either inappropriate or inadequate: the first group has tumour recurrence in the neck after a previous radical neck dissection, and in the second group fixation of the nodal mass to certain underlying structures makes complete clearance unattainable. External beam irradiation is then indicated, but if this modality has already been employed it cannot be used effectively again and the patient may become labelled 'untreatable' or be offered cytotoxic chemotherapy, which is seldom of benefit in this situation.

Interstitial irradiation (brachytherapy) is the surgical implantation of radioactive sources within or around a tumour residuum. Compared with external beam irradiation it offers an advantage in delivering a high local dose with rapid fall-off outside the small treatment volume, thus reducing the dose to normal tissues. Such treatment of malignant neck nodes has been documented for many years[3,4] and the possibility of re-irradiating previously treated areas in this way has been investigated[5–7], although the incidence of tissue necrosis rises rapidly with increasing treatment volume[7,8].

The combination of surgical debulking of the tumour with immediate interstitial implantation may well offer the best opportunity of gaining local control in some unresectable neck recurrences. The advent of large one-stage cutaneous or myocutaneous pedicled flaps now makes possible the excision of skin overlying the implanted area already damaged by previous external irradiation and its replacement by a non-irradiated flap. This not only facilitates healing but also minimizes the risk of soft-tissue necrosis.

Patients and methods

Patients were selected for this treatment only after failure of external beam radiotherapy and radical neck dissection, or when a neck mass was found to be incompletely resectable at the time of surgery. Their clinical details are summarized in *Table 1*.

Case 6 illustrates the use of the technique. After radiotherapy (50 Gy) and surgery (excision of a primary squamous-cell carcinoma of the right floor of mouth with an incontinuity right-sided radical neck dissection) the patient developed an ipsilateral supraclavicular recurrence 8 months later. This was surgically explored and as much of the tumour as possible was removed, a right deltopectoral flap being raised to resurface the skin defect. The nylon tubes to be after-loaded with ^{192}Ir were then positioned (*Figure 1*) after which the skin flap was transposed into the defect and sutured in place. Commercially available 17 gauge steel needles are used to introduce nylon tubing of similar diameter[9] to cover the region of the tumour bed or residuum to be treated, according to the rules specified in the Paris system of dosimetry[10]. These state that the tubes should lie equidistant and parallel to each other and must be loaded with iridium of uniform activity. The distance between the wires (and planes of wires if a double-plane implant is inserted) is approximately 1·5 cm depending on the dimensions of the implant. Orthogonal radiographs are taken to assess the real positions attained, first having loaded the tubes with radio-opaque 'dummies' (this is done postoperatively). The isodose distributions can then be calculated (*Figure 2*). It is helpful to mark the tumour target volume with inactive gold grains to aid localization on planning radiographs and, when possible, to suture the nylon tubing to underlying tissues in the central part of the tumour bed in order to maintain parallelism. The active iridium wire is cut to the specified lengths and placed in nylon sleeves which are then loaded into the tubing in the patient 4–7 days postoperatively, so that wound healing is not compromised. In patients who have previously received radical irradiation, our practice is to

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Table 1 *Clinical details of eight patients*

Case	Age and sex	Site, stage and pathology of primary	Treatment of primary	Interval to neck recurrence	Implant dose (total dose): resurfacing	Site of further recurrence	Survival post implant
1	38 F	Supraglottis T_2N_0 squamous	Chemotherapy + RT (65 Gy)	7 years	46 Gy (111 Gy) No resurfacing: skin necrosis	2 years later at implant margin	30 months A/D
2	65 M	Nasopharynx T_2N_1 squamous	RT (60 Gy)	18 months	40 Gy (100 Gy) No resurfacing: skin necrosis	$2\frac{1}{2}$ years later: outside implant area + pulmonary	54 months D/D
3	76 M	Supraglottis T_2N_0 squamous	Laryngectomy RT (40 Gy)	24 months	49 Gy (89 Gy) No resurfacing: skin necrosis	None	30 months D/DF (MI)
4	57 M	Supraglottis T_3N_0 squamous	Laryngectomy RT (60 Gy)	18 months	45 Gy (105 Gy) Pectoralis major flap: no necrosis	None	12 months A/DF
5	65 M	Transglottic T_3N_1 squamous	Laryngectomy, RND RT (60 Gy)	6 months	43 Gy (103 Gy) Pectoralis major flap: no necrosis	9 months later: outside implant area + pulmonary	11 months D/D
6	51 F	Floor of mouth T_2N_1 squamous	Excision, RND RT (50 Gy)	8 months	40 Gy (90 Gy) Deltopectoral flap: no necrosis	6 months later: outside implant area	12 months D/D
7	63 M	Anterior tongue T_1N_1 squamous	RT (60 Gy) Excision (after referral)	22 months	60 Gy (120 Gy) Local rotation flap: no necrosis	Pulmonary: noted at time of implant	6 months D/D
8	58 F	Right neck T_0N_3 adeno occult primary	RT (28 Gy) RND	Immediate	32 Gy (60 Gy) Pectoralis major flap: no necrosis	Persistent disease throughout	9 months D/D

RND, radical neck dissection; RT, external beam radiotherapy; A/D, alive with disease; D/D, dead with disease; D/DF, dead, disease-free; A/DF, alive, disease-free; and MI, myocardial infarct

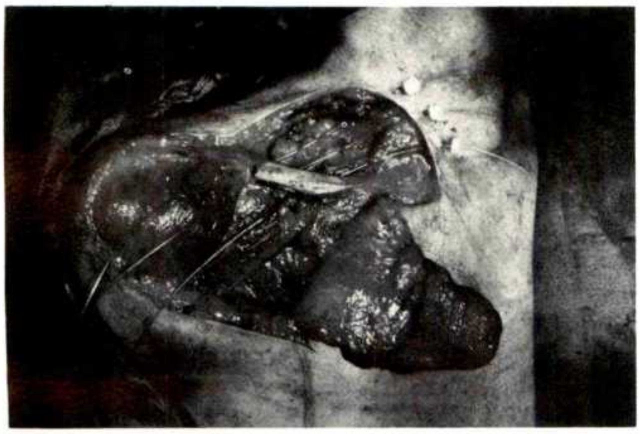

Figure 1 *The deltopectoral flap has been raised and the nylon tubes inserted so as to lie across the tumour bed*

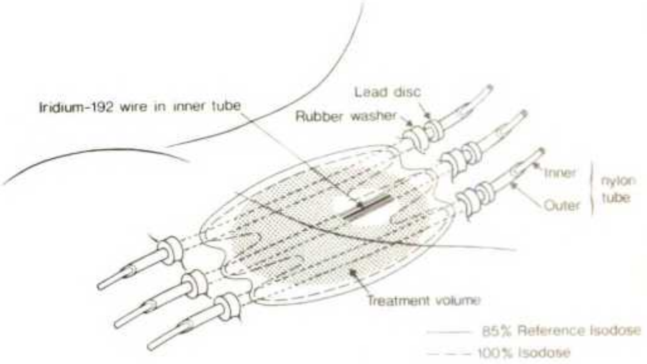

Figure 2 *Diagrammatic representation of the implant showing details of the arrangement of the tubes and of the treatment volume*

prescribe 40–50 Gy to the reference 85 per cent isodose (essentially the minimum dose delivered to the target volume) to be given over 4–6 days. The patient is nursed in a side ward which conforms to radiation protection requirements, and nursing and visiting times are restricted to the approved limits calculated from the total activity of the iridium implanted. Active wires and tubing can be removed on the ward without an anaesthetic.

Results (see *Table 1*)

Of the seven patients with recurrent squamous carcinoma, four had control of their disease in the implanted area for their remaining lifespan (6–54 months), one remains disease-free at 1 year while the other two developed recurrent disease at the margins of the treatment volume. Three of these patients developed malignant lymphadenopathy at other sites in the neck, one developed recurrent disease at the primary site and distant metastases were detected in three cases. One patient died of a myocardial infarct, apparently disease-free, 2·5 years after surgery and implantation, and a further patient remains disease-free 1 year after implant. The other five patients died from recurrent disease. A single patient (case 8) with an adenocarcinoma never had her neck disease controlled despite a radical neck dissection, external beam irradiation and interstitial implantation.

Of the five patients (cases 4–8) who had flap resurfacing at the time of implantation (total combined external beam and implant doses of 60–120 Gy) none developed soft tissue necrosis, whereas all patients (cases 1–3) who did not undergo resurfacing (total doses of 89–111 Gy) developed local soft-tissue breakdown. Surgical repair of the surface defect was required in only one case, the other two are healing slowly with conservative management.

Discussion

Although a radical neck dissection is usually successful in clearing mobile metastatic cervical lymph nodes, this may not be the case when the nodal mass is fixed. Strong[11] and Beahrs[12] report recurrence rates of 36·5 per cent and 26·5 per cent respectively in patients with fixed nodes. The actual rate will depend on a variety of factors but most studies report rates over 25 per cent for such patients, even if radiotherapy has been used in conjunction with surgery[13].

The finding of an unresectable mass at the time of a radical neck dissection or tumour recurrence after a neck dissection are two problems for which conventional treatment options are inadequate. Santos[14] commented on the lack of specific discussion in the literature regarding the role of surgery in the management of head and neck carcinomas with fixed nodes, and asserted that surgery does not play a substantial part in improving the survival rates of such patients. However, if no effective treatment is offered to the patient, then death occurs from distressing cervical disease and we believe it reasonable to offer palliative, or possibly curative, therapy to make the patient more comfortable by control of regional disease, and with a chance of producing prolonged disease-free survival.

The rationale behind the use of interstitial irradiation by implantation is that re-treatment with irradiation can be given to the limited volume of tissue containing the residual disease, with a rapid fall-off in dosage permitting tumour control while minimizing damage to adjacent normal structures. The continuous low dose given by the implant may also be advantageous over the intermittent high dose rate treatment given by external beam units. Pierquin[5] reported the results of salvage implant without surgery in 124 cases of inoperable neck node recurrences. Substantial tumour regression occurred in 57 per cent of patients, with complete response in 25 per cent. For control, doses of the order of 60 Gy are required and the risk of tissue necrosis is considerable, particularly when the volume of implanted tissue increases as nodal size exceeds 3 cm diameter. Syed[7] reported irradiation-induced complications in 30 per cent using ^{192}Ir, although this figure may be reduced by using iodine-125 seeds which produce irradiation of lower penetration[15]. The combination of macroscopic surgical clearance or substantial debulking, which permits the delivery of lower doses of irradiation (40–50 Gy), and the use of skin flaps to resurface the area, significantly reduces the risk of radionecrosis. Fortunately, the carotid artery is a radioresistant structure and its rupture is far more likely to be due to persistence of tumour than to irradiation damage. The after-loading iridium wire technique is preferred to permanent implants, such as gold grains or radioactive suture material[16], because the dosimetry can be calculated with far greater accuracy and remains under the control of the radiotherapist or surgeon throughout the treatment period. After-loading also obviates exposure of theatre staff to the radiation source.

Future developments might include the combination of interstitial irradiation with hyperthermia[17], particularly in those cases which have appeared to be resistant to external beam irradiation.

Salvage surgery with interstitial implantation, or brachytherapy, must be regarded in most cases as palliative, the patient being unlikely to be cured of his cancer[18]. Nevertheless, the technique can provide a prolonged symptom-free period of disease control and occasional cure. Left untreated, these nodal metastases invariably become progressively more painful and distressing.

Combined surgery and postoperative interstitial irradiation is a technique which is easily available to any multidisciplinary Head and Neck Unit and is worthy of consideration in patients with a technically unresectable but limited metastatic nodal mass in the neck, but preferably with disease control at other sites.

Acknowledgements

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Use of myocutaneous flaps for primary cover following lymph node dissection for malignant melanoma

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We report seven patients undergoing palliative surgery for advanced malignant melanoma, who required wide excision of skin and underlying tissue in association with lymph node dissection. In each case, primary closure of the wound was facilitated by the use of a myocutaneous flap. Four ilio-inguinal lymph node dissections were closed with rectus abdominis flaps, two cervical dissections were closed with a pectoralis major flap, and a limited latissimus dorsi flap was used for one axillary clearance. Primary healing was achieved in all cases; morbidity was low, with one wound infection and two limited lymphatic collections. All donor sites were closed primarily and healed well. We conclude that in selected patients the use of a myocutaneous flap procedure gives excellent coverage of large defects with low morbidity. In particular, there is rapid convalescence and return of good function after palliative resections, while the wide excision minimizes local recurrence where the tumour is in proximity to overlying skin.

Keywords: Melanoma, lymph node dissection, myocutaneous flaps

Despite an extensive literature on the primary surgical management of cutaneous malignant melanoma and the treatment of lymph node involvement, much controversy remains in both areas. Many aspects of current primary management are reviewed in a recent paper[1]. There is little doubt that therapeutic block dissection is a beneficial method of treatment, but its efficacy is dependent on wide tissue excision. The incidence of in-transit secondary deposits is decreased by in-continuity dissection to 2 per cent as compared with 14 per cent after a discontinuous procedure[2], so an in-continuity procedure is preferred where feasible. Where advanced nodal disease, involving or in proximity to the overlying tissue, dictates a palliative procedure, extensive excision of skin and underlying tissue is necessary to achieve low local recurrence rates and the benefit of surgery may be lost unless primary healing and rapid restoration of function are achieved. There are some situations where this is best achieved by myocutaneous flap repair but there has been little discussion of this aspect of melanoma surgery. We report a small series of patients which illustrates the indications and results of this adjunctive technique.

Patients and methods

The seven patients reported here (*Table 1*) had disease limited to the regional lymphatic tissues with no evidence of distant spread. An unusually wide excision of soft tissue was necessary because of involvement of subcutaneous tissue and/or skin, making direct primary closure impossible. Both cervical clearances were second operations, the four inguinal dissections were for advanced nodal disease (one post-radiotherapy, one very extensive in-continuity dissection) and the axillary dissection required excision of a large skin area to clear the scar of a previous exploration. In the cervical and axillary dissections with wide excision of skin, the underlying neurovascular structures require more substantial coverage than that provided by split-skin grafting. During the period of this study, 79 patients underwent conventional node dissection for melanoma.

Flaps used

The flaps used are shown in *Table 1*. The anatomy and techniques of each are well described in standard publications[3]. Two modifications of the standard flaps were used. The first was an extended rectus abdominis flap which allowed primary filling of a defect almost to the knee[4]. The muscle element of the latissimus dorsi flap was limited in size to the area of the skin island required.

Complications

No flap was lost in part or in whole. One patient developed a wound infection along one edge of a rectus flap in the groin but this healed with conservative management. Two lymphatic collections required aspiration but did not delay discharge. No thrombo-embolic or chest complication was seen, with the possible exception of case 5.

Results

Illustrative cases

Case 1: Extended rectus abdominis flap for palliative, in-continuity excision. Patient 1 presented with a very large fungating melanoma on the lower medial thigh with massive nodal involvement. The disease was unresponsive to chemotherapy. The disease was clearly incurable but it was felt that short-term palliation could best be achieved by radical excision of the primary lesion and involved nodes with removal of a wide strip of intervening skin (*Figure 1*). The defect was repaired with an extended ipsilateral rectus abdominis flap as described by Taylor[4] (*Figure 2*), the extension being taken almost to the axilla. Rapid cover and healing was obtained and local control achieved in the leg, until death occurred from abdominal and disseminated disease 16 months later. This case illustrates filling of a very large defect with good local control and rapid convalescence, optimizing the quality of life during the short remaining life expectancy.

Case 2: Insertion of flap into the axilla to maintain shoulder mobility. Patient 2, a 54-year-old man, was referred from his local hospital having recently undergone a left axillary exploration for an enlarged lymph node which was histologically involved with malignant melanoma. No primary lesion could be identified. He subsequently underwent an extrafascial axillary dissection with wide excision of axillary skin necessary to allow full clearance of the recent incision scar and undermined skin flaps (*Figure 3*). The defect was covered with a latissimus dorsi myocutaneous flap limited to the anteromedial aspect of the muscle (*Figure 4*). Two of the excised nodes

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Table 1 *Patients, procedures and clinical course*

	Age	Sex	Primary site	Primary depth	Procedure	Flap used	Follow-up	Reason for use of a flap repair
1	67	M	Right thigh	1·5 mm	Ilio-inguinal	Right rectus with extension	Well at 2 months, died of disseminated disease at 16 months	Advanced disease, wide excision in continuity
2	54	M	No primary detected	—	Axillary	Latissimus dorsi	Disseminated disease at 14 months	Tissue replacement to give arm mobility
3	67	F	Left calf	1·5 mm	Ilio-inguinal	Right rectus abdominis	Died at 4 weeks	Fungating nodes and local radionecrosis
4	69	M	No primary detected	—	Cervical	Pectoralis major	No local recurrence, died of cerebral deposits at 9 months	Extensive recurrence following local excision
5	67	F	Right calf	2 mm	Ilio-inguinal	Right rectus abdominis	Well with recurrence distant at 17 months	Advanced inguinal nodes, gross obesity
6	42	F	Left calf	3·1 mm	Ilio-inguinal	Right rectus abdominis	Well without recurrence at 5 years	Large node mass
7	63	M	Right side of neck	6 mm	Cervical	Right pectoralis major	Died at 15 months	Safe cover of carotid vessels

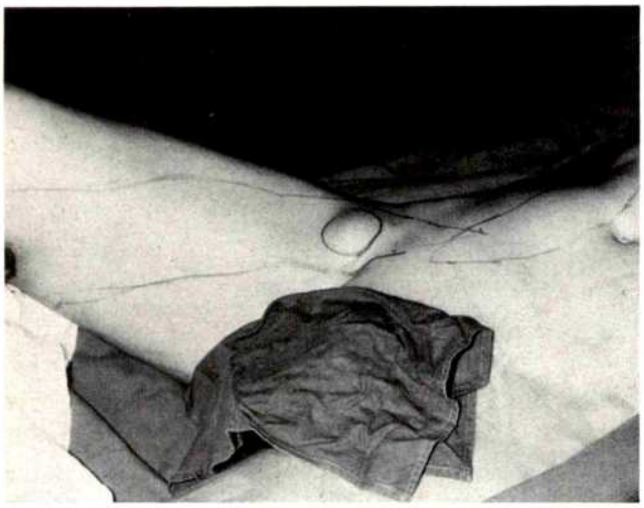

Figure 1 *Pre-operative skin markings for wide in-continuity excision of advanced primary melanoma with large inguinal node by ilio-inguinal lymph node dissection with extended rectus abdominis flap*

contained malignant melanoma. A small fluid collection required aspiration, but did not delay his discharge. This case illustrates the use of a myocutaneous flap to cover vital neurovascular structures and to provide soft tissue replacement for shoulder mobility.

Case 3: Myocutaneous flap coverage for palliative excision following radiotherapy. Patient 3, a 67-year-old woman, underwent excision of a 1·5 mm thick malignant melanoma on the medial side of the left calf. She refused follow-up, but returned 6 years later with an 8 × 5 cm necrotic mass in the left groin, which persisted after radical radiotherapy for involved nodes (*Figure 5*). Incisional biopsy confirmed active melanoma but no distant disease could be detected. A radical palliative ilio-inguinal lymph node dissection was performed because of pain, bleeding and discharge, and the defect was closed as a primary procedure with a contralateral rectus abdominis myocutaneous flap (*Figure 6*). The patient made a good recovery but died suddenly 4 weeks later, presumably of cardiac or pulmonary disease. This patient probably had residual disease around the femoral vessels. In this situation the thickness of normal flap tissue over any residual disease is likely to give prolonged local control, as well as giving good healing after extensive radiation tissue damage.

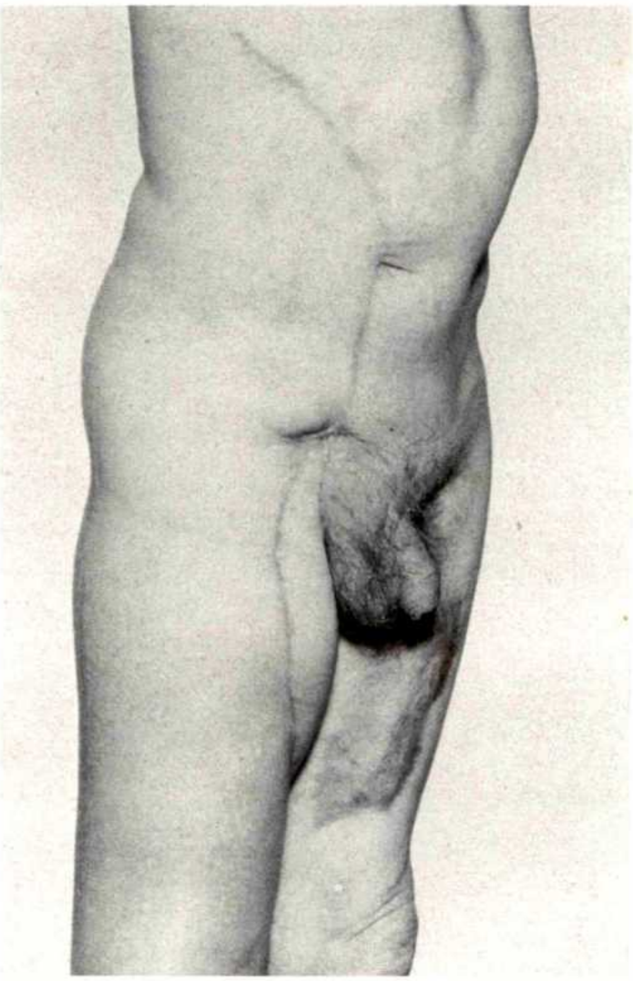

Figure 2 (case 1) *Appearance at 3 months showing flap and primary healing of donor wound*

Discussion

In 1973 McGregor and Morgan[5] gave an account of axial and random pattern flaps. The search for suitable donor flaps with predictable blood supply has since progressed rapidly and cutaneous, myocutaneous and more complex flaps are widespread in plastic and reconstructive surgical practice[6–9].

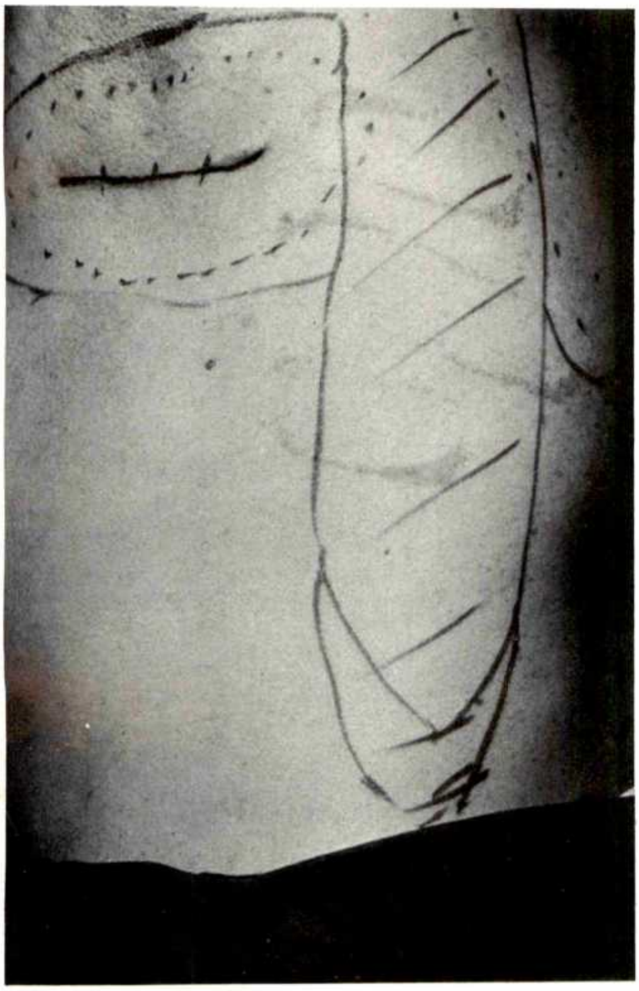

Figure 3 (case 2) *Skin markings at operation showing recent exploratory excision, extent of bruising and potential contamination (dotted line)*

General surgeons have also found myocutaneous flaps useful, especially in breast reconstruction following mastectomy but also in other areas[10,11].

Myocutaneous flaps have many advantages over pedicle flaps or split-skin grafts which would be the alternative methods of cover in many cases. The most important from the patients' viewpoint is completion of the procedure in one session without a painful donor area or subsequent increasing scarring at the graft site.

There are a number of important advantages for the surgeon. Flaps provide good healing potential in areas of poor blood supply, e.g. postradiotherapy, and in areas prone to infection as in groin wounds. The extensive skin defects resulting from adequate skin excision to provide local control of advanced disease can be covered without closure under tension or recourse to delayed repeated grafting procedures. In palliative cases this delay may take up most of the patient's remaining life. Other important advantages include a thick tissue cover to minimize local symptoms if there is unrecognized residual disease, and early return of function. When major neurovascular structures are exposed during dissection and the overlying skin has to be excised then a myocutaneous flap provides immediate reliable cover.

Excellent results have been achieved by local cutaneous flap coverage after excision of primary malignant melanomas[12,13]. These random pattern or even fasciocutaneous flaps are useful for restricted excision but cannot always provide large areas of cover. As microvascular techniques have improved, free myocutaneous flaps are possible from most recognized donor sites such as the rectus or latissimus dorsi[14,15], and are useful where no direct flap is available.

The width of clearance of involved nodes, and the use of in-continuity dissection, is a matter of some controversy. Primary closure is usually possible when disease is confined to the nodes, though local recurrence can be a problem[16]. Where there is extracapsular spread, or prior conservative dissection has

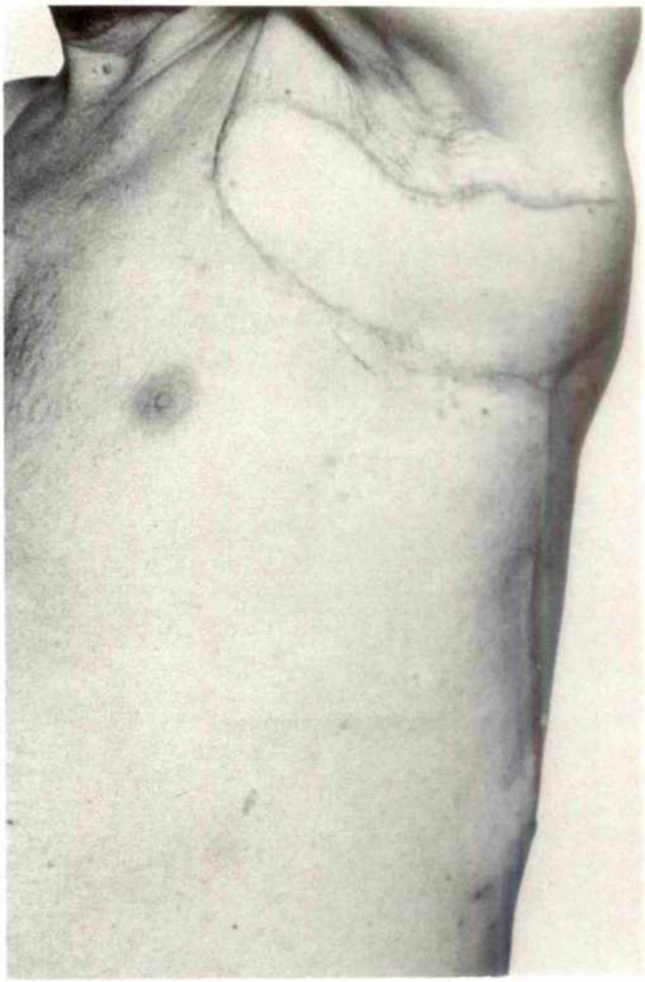

Figure 4 (case 2) *Donor and recipient scars at 8 weeks, with full shoulder mobility*

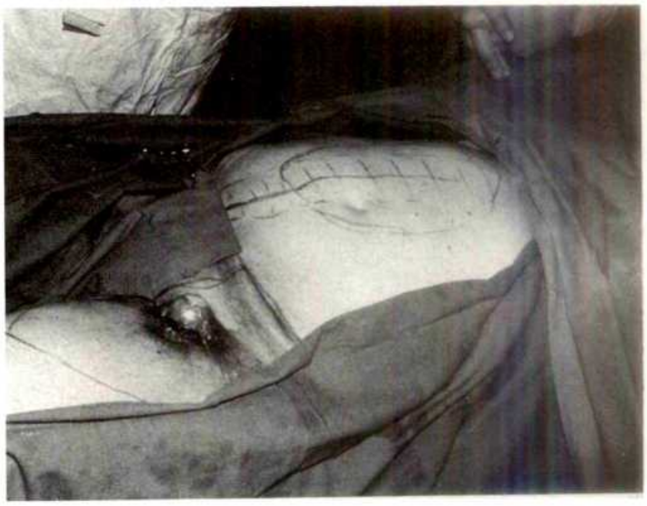

Figure 5 (case 3) *Fungating nodes in left groin. Operative marking to show extent of skin and tissue excision and outline of contralateral rectus abdominis flap*

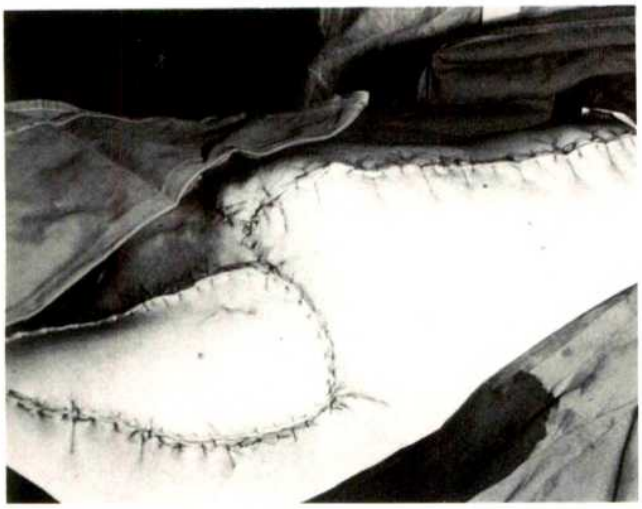

Figure 6 (case 3) *Immediate postoperative appearance. (In the absence of radiotherapy we would now prefer an ipsilateral flap as in case 1)*

contaminated undermined skin flaps, it is generally accepted that wide excision of skin is necessary. Our routine is to clear advanced nodes by at least 4 cm, and to excise completely wounds that may have been contaminated with tumour cells. Some support for this approach may be taken from the absence of local recurrence in these seven high-risk cases. Secondary referral for local recurrence after more conservative node dissection regularly occurs in our practice. In-continuity dissection for melanoma decreases local recurrence[2] and most surgeons recommend this where the distance is 20 cm or less. In-continuity dissection over a longer distance, as in case 1, is more controversial. Local recurrence after inguinal node dissection is usually at the apex of the dissection[17], while in-transit metastasis is almost always in the direct line of the lymphatics. Hence the procedure has some logic where the chance of in-transit recurrence is high, especially when reconstructive techniques allow primary healing.

A second cause of concern has been that the thickness of myocutaneous flaps may delay detection of local recurrence. This may be advantageous in a patient where palliation of local symptoms is the prime consideration but may be disadvantageous if early detection in a potentially curable case is delayed. Following radical excision, however, local recurrence is usually an indication of disseminated disease. In the type of patient under discussion here, effective treatment is unlikely to be available for recurrence, so delayed recognition of local recurrence may be positively advantageous. Certainly, neither of the problems has been found in this series. Any theoretical disadvantage is outweighed by the decreased risk of recurrence after the wise tissue excision made possible by easy reconstruction, while rapid convalescence and return of function adds to the patient's quality of life.

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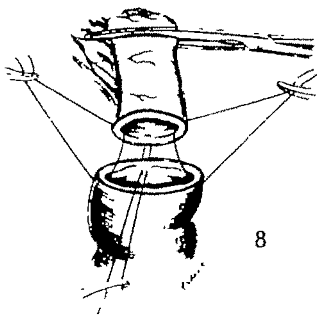

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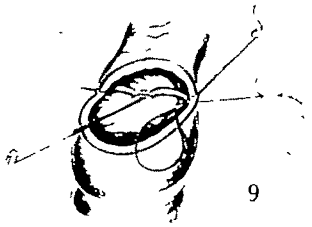

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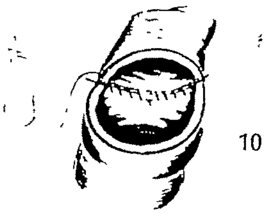

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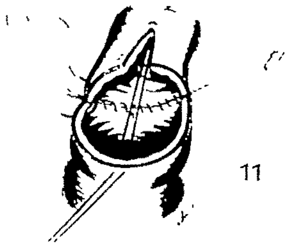

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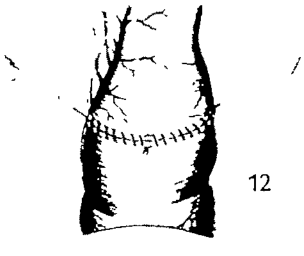

12

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Acral (volar-subungual) melanoma in Auckland, New Zealand

We have retrospectively reviewed the charts of 34 acral melanoma patients (melanoma arising from the volar skin of the hands, feet or a subungual site) seen in the Auckland area between 1970 and 1985. These 34 patients constituted 3·5 per cent of the total number of patients (972) reviewed over this period. Six of the thirty-four patients were either Polynesian or Maori. There were 19 men and 15 women, and the mean age of the group was 59 years. The primary lesion arose from the plantar or palmar skin in 25 patients and 9 patients had subungual lesions. All lesions but one were pigmented. Most patients with plantar or palmar lesions presented with clinical stage 1, Clark's level 4 disease, while those with subungual lesions presented most commonly with stage 2, Clark's level 5 disease. Treatment was wide local resection for plantar and palmar lesions and amputation for subungual lesions. Regional lymph node dissection was performed in 10 patients with positive nodes at presentation and in 6 patients who developed metachronous nodal disease. Patients were followed for between 1 and 16 years, and 18 patients died in this period, 15 of metastatic melanoma (mean time 34 months). Subungual melanoma carried a worse prognosis than melanoma arising in palmar or plantar skin.

Keywords: Malignant melanoma, volarsubungual melanoma, acral lentigenous melanoma, surgical treatment

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Acral melanoma is a distinct variant of malignant melanoma, occurring at the periphery, on the volar surface of the hands, feet, fingers, toes and subungual sites[1]. In the early 1970s Reed[1] characterized this unusual melanoma histologically and introduced the term acral lentigenous melanoma (ALM). Recently several investigators have reported 5-year survival rates of under 40 per cent for acral melanoma[2,3] indicating that the prognosis of this type of melanoma is worse than melanoma in other sites. Malignant melanoma is common in New Zealand compared with the incidence seen in most other countries with the exception of Australia[4]. However, despite several series of malignant melanoma being reported from New Zealand, there has been no specific review of this curious malignancy. In particular, acral melanoma is more common in non-Caucasians[8,9], but the incidence of this condition in the New Zealand Maori and Polynesian population has not been defined. Accordingly we have retrospectively reviewed the 34 patients who have presented with acral melanoma in the Auckland area between 1970 and 1985.

Patients, methods and results

Clinical data

A total of 972 charts of patients with the diagnosis of malignant melanoma seen in the public hospitals of the Auckland area from 1970 to 1985 were reviewed following a search of the local cancer register. Of these patients, 34 had primary melanomas located on either the palm, sole, volar skin or nail bed, thereby accounting for 3·5 per cent of the total. The clinical details of these patients are summarized in *Table 1*: there were 19 women and 15 men. The patients' ages ranged from 23 to 90 years with a mean age of 59 years Seven of the thirty-four patients were non-European· three Maori, three Polynesian and one Chinese.

Location of the primary lesion

The location of the primary neoplasm was plantar in 24 patients; five arose from the skin of the heel, thirteen from the remaining plantar skin and six others from the volar skin of the toes. No patient had a primary lesion of the palmar skin, but one patient presented with a primary melanoma of the volar skin of the thumb. Subungual melanoma was found in the toe of five patients, and in the finger in four patients.

Gross appearance

Plantar/palmar lesions. The lesions ranged from 0·5 cm to 4 cm in diameter. They were dark brown or black and had irregular borders. Fifteen out of twenty-five patients in this group had ulcerated primary lesions at the time of presentation, and one lesion was amelanotic

Subungual lesions. All nine patients presented with a dark brown 'spot' in the nail bed, and in four patients the nail bed had split and the tumour had ulcerated through the nail plate.

Duration of symptoms to diagnosis

In 13 patients there was delay between the onset of symptoms and presentation, but in all but 1 patient there was negligible delay between presentation and diagnosis of the primary lesion. Malignant melanoma was not recognized initially in one patient, the initial diagnosis being an ischaemic leg ulcer.

Biopsy

Diagnosis was made by excision biopsy, which in the case of the subungual lesions was preceded by removal of the nail.

Microscopic findings

Plantar/palmar. In five patients the histological material was inadequate for detailed histological evaluation because of severe necrosis and ulceration. The level of invasion according to Clark's classification[10] could be determined adequately in only 20 of the 25 patients. Three lesions were level 2, four were level 3, ten were level 4, and in three the tumour had invaded the subcutaneous fat or periosteum (Clark's level 5).

Subungual. In six patients the histological material was inadequate for complete histological evaluation because of necrosis and ulceration. The level of invasion according to Clark's classification could be adequately determined in only six of the nine patients with subungual lesions. Four patients had lesions that extended into the periosteum and subcutaneous fat (level 5), while two patients had level 4 lesions

Staging

The patients were all staged clinically as stage 1–3.

Plantar/palmar. Nineteen patients had no evidence of regional nodal or distant metastatic disease on presentation and were classified as

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Table 1 *Clinical details of patients*

No.	Sex*	Age (years)	Race†	Location of primary‡	Clark's level of invasion§	Clinical stage at presentation	Ulceration of primary lesion	Local treatment¶	Nodal status//	Disease-free period	Time to regional metastases	Time to distant metastases	Survival #
1	M	90	E	Plantar	V	1	+	WLE	Negative	1 year			A 1 year
2	F	58	E	Plantar	IV	1	+	WLE	Negative	2 years			A 2 years
3	F	70	E	Plantar	IV	1	–	WLE	Negative	3 years			A 3 years
4	F	50	E	Plantar	II	1	–	WLE	Negative	14 years			A 14 years
5	F	79	E	Plantar	IV	1	–	WLE	Negative	6 years			A 6 years
6	F	23	E	Plantar	III	1	–	WLE	Negative	4 years			A 4 years
7	M	55	E	Plantar	UM	2	+	WLE	Positive TGD	2 months	2 months^{+}	10 months	D 1 year↑
8	M	57	P	Plantar	II	1	–	WLE	Negative	1 year			D 2 years
9	F	61	E	Plantar	II	3	+	WLE	Positive TGD	0 months	0 months	0 months	D 8 months↑
10	F	87	E	Plantar	IV	1	+	WLE	Negative	2 years 5 months			D 2 years 5 months
11	F	73	E	Plantar	IV	1	+	WLE	Negative	18 months		18 months	D 21 months
12	F	78	E	Plantar	III	1	+	WLE	Negative	2 years			A 2 years
13	F	55	E	Plantar	III	2	+	WLE	Positive TGD	1 month		1 month	D 2 years↑
14	M	62	E	Heel	IV	1	+	WLE	Negative	6 years			A 6 years
15	M	28	E	Heel	IV	3	+	WLE	Positive TGD	0 months	0 months	0 months	D 2 years↑
16	M	62	E	Heel	IV	1	+	WLE	Negative	10 months			D 1 year↑
17	F	69	P	Heel	V	1	+	WLE	Negative	4 years			A 4 years
18	F	56	E	Heel	UM	3	+	WLE	Positive TGD	0 months	0 months	0 months	D 1 year
19	M	52	E	Toe (SU)	IV	1	–	AMP	Negative	6 years			A 6 years
20	F	61	P	Toe (SU)	UM	3	+	AMP	Positive TGD	0 months		0 months	D 2 months↑
21	M	44	MO	Toe (SU)	UM	2	+	AMP	Positive TGD	30 months	30 months		AWD 5 years
22	M	54	MO	Toe (SU)	V	1	+	AMP	Negative	1 year			A 1 year
23	M	68	E	Toe (SU)	IV	1	+	AMP	Negative	5 years			D 8 years↑
24	M	64	MO	Finger (SU)	UM	2	–	AMP	Positive TAD	0 month			D 6 months↑
25	F	82	E	Finger (SU)	V	2	–	AMP	Positive TAD	9 months		9 months	D 12 months↑
26	M	36	E	Finger (SU)	V	1	–	AMP	Negative	2 years			A 2 years
27	F	47	O	Finger (SU)	V	1	–	AMP	Negative	21 months		21 months	D 3 years↑
28	M	30	E	Toe	IV	2	+	AMP	Positive TGD	5 months		5 months	D 14 months↑
29	M	78	E	Toe	IV	2	+	AMP	Positive TGD	5 months		5 months	D 14 months↑
30	F	53	E	Toe	UM	1	–	AMP	Negative	7 years 8 months			D 7 years 8 months
31	F	58	E	Toe	UM	1	–	AMP	Negative	15 years	15·2 years^{+}	16 years	D 16 years 4 months
32	F	26	E	Toe	III	1	–	AMP	Negative	12 years			A 12 years
33	F	84	E	Toe	V	1	+	AMP	Negative	1 year			D 23 months↑
34	M	50	E	Finger	UM	1	–	AMP	Negative	4 years			A 4 years

Key: *M, male; F, female; †E, European New Zealander; P, Pacific Island Polynesian, MO, New Zealand Maori; O, other; ‡SU, subungual; §UM, unclassifiable melanoma; ¶WLE, wide local excision; AMP, amputation; // Negative, negative lymph nodes; Positive, positive lymph nodes; TGD, therapeutic groin dissection, TAD, therapeutic axillary dissection; #D, dead; A, alive; AWD, alive with disease; +, plus local recurrence of disease; ↑, died of disseminated melanoma

clinical stage 1. Three patients had palpable regional nodes on admission and were classified as stage 2, and three patients were found to have distant metastases in either lung, liver, spleen or bone at the time of presentation and were therefore classified as stage 3.

Subungual. Five patients presented with no evidence of nodal or distant spread and were classified as clinical stage 1; three patients had palpable regional lymph nodes on presentation, and were classified as stage 2, while one patient had widespread metastatic disease and was classified as stage 3.

Surgical treatment

Local treatment. All patients had excision of the primary lesion for local control. Lesions of the plantar skin were excised with wide margins (average margin 3 cm) down to the deep fascia and repaired with a split-skin graft. Patients with lesions of the fingers and toes (either subungual or volar) were treated with digital amputations either one or two joints proximal to the lesion

Regional lymph node dissection. Prophylactic nodal dissection was not performed in any patient. Therapeutic groin dissections were performed in the nine patients with inguinal nodal disease and axillary dissection was performed in the two patients who presented with palpable axillary nodes.

Follow-up

The patients were followed for between 1 and 16 years and 15 patients died of metastatic melanoma within this time interval (the mean time from diagnosis to death being 34 months). All four patients with stage 3 disease died within 2 years of diagnosis. Nine of the ten patients who had therapeutic block dissections for regional nodal disease (five patients were stage 2 on admission), died within 2 years of presentation, while one patient with stage 2 disease is alive with disease at 5 years. The mean time from diagnosis until death for the 6 patients who died with stage 2 disease was 13 months.

Of the 23 patients with stage 1 disease, 15 are alive between 2 and 14 years after diagnosis; 3 died between 2 and 8 years after diagnosis from causes unrelated to malignant melanoma, while 2 patients who presented with stage 1 disease developed metastases at 12 months and 15 years, respectively, after diagnosis and died of disseminated melanoma after 3 years and 16 years respectively.

Of the 24 patients with plantar lesions, 11 were alive between 1 and 14 years after diagnosis, while 13 had died between 1 and 8 years following diagnosis. Three of the patients with subungual melanoma were alive between 1 and 6 years after diagnosis. One patient with subungual melanoma was alive with disease (metastases) 5 years after diagnosis, and the other five patients with subungual melanoma all died of melanoma between 6 months and 8 years after diagnosis.

Discussion

The volar skin and the nail bed are infrequent sites of malignant melanoma in Caucasians, accounting for between 2·6 per cent and 7 per cent of the total in a number of series[2,8]; the incidence in New Zealand of 3·5 per cent therefore fits in the spectrum. In dark-skinned races acral lesions are relatively more common[3,5,9,11,12], and our data on Maori and Polynesians are consistent with this finding. Overall, malignant melanoma is rare in New Zealand Maoris and Pacific Island Polynesians, these races constituting only 1·6 per cent of the total[4]. However, when acral lesions are considered as a separate group, 18 per cent of these patients are either Maori or Polynesian.

Acral melanoma is reported to occur predominantly in the older patient in the sixth to eighth decades[8,9,13,14], whereas melanoma in other sites has a peak incidence in the fourth or fifth decade[4]. Our data are consistent with this finding, as 80 per cent of patients presenting with this disease in New Zealand were over the age of 60 years, and only four patients were aged 30 years or younger.

The majority of the primary lesions in this and in other series occurred on the foot, the most common site being the heel in other series[11–13], but in New Zealand other parts of the plantar skin were more often affected. Like other series[2], volar melanomas outnumber subungual melanomas, and in accord with the findings of others, in New Zealand the commonest site of subungual melanoma was the toe[11–13].

As with other reports[12,13], in New Zealand volar lesions were usually heavily pigmented, with a high incidence of ulceration necrosis and bleeding and all, histologically, were advanced, the Clark level of invasion[10] being either 4 or 5.

The diagnosis of acral melanoma is often delayed[11,13–15]. Our findings are consistent with this in that 65 per cent of the patients presented with ulcerated lesions, suggesting late presentation[2], possibly because the plantar skin is kept covered, and overlooked by the patient until the development of bleeding, regional lymphadenopathy, etc. In addition, when noticed early, this lesion can be readily confused with other more common conditions such as digital ischaemia, fungal infections or echymosis[11,12].

In our patients the surgery employed was, in general terms, adequate in that local recurrence was seen in only two of the thirty-four patients. In the patients with subungual lesions the need to obtain a narrowest margin of at least 1 cm[16] necessitated digital amputation, most commonly at the distal interphalangeal joint.

Acral melanoma has a worse prognosis than other limb melanomas, the average reported 5-year survival rate being between 30 per cent and 50 per cent, and the 10-year survival figures are as low as 0–13 per cent[14,17]. Our results reflect this poor survival with 15 of our 34 patients dying of melanoma within 5 years of diagnosis. In addition, the patients with subungual melanoma presented for treatment both with deeper lesions and at a more advanced disease stage than did patients with plantar and palmar lesions. As a result the patients with subungual lesions did less well, 55 per cent dying from disseminated melanoma, *versus* 40 per cent of patients with plantar or palmar lesions. This is in contrast to the finding of McGovern[18] in Queensland, Australia, who reported that although subungual melanomas had a greater average thickness than plantar or palmar lesions, survival was better in the subungual group.

Rapid invasion, ulceration and early metastatic spread are common to most series[11,12,14,19]. Nine of the thirty-four patients in our series had regional or systemic metastases at presentation, this being lower than the reported experience of others[2]. However, a further six of our patients who had clinically negative lymph nodes at presentation died within 5 years, all of proven metastatic melanoma. Most patients with involvement of regional lymph nodes in our series died, on average within 3 years of presentation. There is no doubt that therapeutic lymph node dissection is justified[11–14], because no other treatment is effective in these patients. The role of prophylactic lymph node dissection, however, is less accepted, and this treatment has not been performed in Auckland. Some investigators have indicated that prophylactic lymphadenectomy offers a prognostic and therapeutic benefit[3,8,9,20] and Gutman *et al.*[2] found micrometastases in two out of seven patients in whom prophylactic nodal dissections were performed, suggesting that acral melanoma spreads to regional lymph nodes early. Isolated limb perfusion with high-dose chemotherapy and hypothermia has been shown to be an effective modality when combined with surgical excision[11,14,20,21] and prospective studies addressing the place of this type of treatment in an adjuvant setting are currently in progress. The use of adjuvant limb perfusion for acral melanoma has not, however, been employed in Auckland.

In summary, our series of patients emphasizes that, in New Zealand, acral melanomas are rare lesions in Caucasians, being relatively more common in Maoris and Polynesians. The outlook for acral lesions is poor: 44 per cent 5-year survival for acral *versus* 69 per cent 5-year survival for melanomas overall[4]. Significant prognostic factors in acral melanomas, as in melanomas affecting other sites, are the presence of regional or distant metastases and ulceration of the primary lesion. Early detection and wide local excision remain the cornerstones of management. In view of the high incidence of synchronous and metachronous nodal disease, it is important that the role of prophylactic lymphadenopathy and adjuvant limb perfusion be further clarified in this particularly aggressive subtype of melanoma.

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Case report

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72

Omental viability and incisional herniation after omental transposition for the repair of chest wall defects

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Exteriorized transposition of the greater omentum is a useful technique for covering the extensive defects which may follow mastectomy for locally advanced cancer or radionecrosis[1–6].

We report two patients who developed small bowel obstruction due to incisional hernias along the pedicle of the exteriorized greater omentum, in whom it was not possible to divide the omental pedicle to allow a complete repair.

Case reports

The first patient, aged 77 years, had been treated by lumpectomy and radiotherapy for a stage 1 breast cancer. She had received 55 Gy in 17 treatments over 67 days Seven years later she developed painful ulceration of the breast with discharging sinuses. Biopsy showed no evidence of recurrent tumour and the mastectomy specimen revealed changes of radionecrosis.

The second patient, aged 53 years, presented with a locally advanced breast cancer treated primarily by radiotherapy. She received 59 Gy in 27 treatments over 56 days. Sixteen months later she underwent mastectomy for local recurrence and ulceration.

In both cases laparotomy was performed through an upper midline incision. The omentum was mobilized on both gastro-epiploic pedicles and taken up to the chest wall through a separate muscle-cutting incision in the upper lateral part of the left rectus abdominis. The omentum was covered by meshed split skin grafts, and primary healing was achieved.

Both patients later presented with intestinal obstruction, the first at 5 months and the second at 7 months postoperatively. At exploration defects measuring 10 × 5 cm were found in both cases. The omental pedicles were defined and occluded with non-crushing clamps. In both patients the skin grafts became dusky within minutes and it was not considered safe to divide the pedicles. The defects were repaired by polytetrafluoroethylene patches cut to form keyholes around the pedicles.

Discussion

Incisional herniation is a recognized complication of exteriorized omental transposition. It is said to be less common when the pedicle is led through a separate incision in the rectus than when it is taken through the upper end of the midline abdominal wound[6]. Recently, excision of the xiphisternum has been found to provide a satisfactory route for the pedicle through the cranial end of the upper midline incision (H. White, unpublished results). The pedicles may have been unusually bulky in these cases as both epiploic vessels were preserved to ensure a good blood supply.

It has been stated that the omental pedicle may be safely divided after 3 months[5], or earlier if a period of intermittent clamping is practicable[3,7]. The present cases illustrate the need for considerable caution in dividing the omental pedicle; preliminary soft clamping would appear to be a wise precaution. It is possible that the extensive radiotherapy in these cases reduced the omentum's capacity to acquire a secondary blood supply.

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Effect of epidural anaesthesia on intestinal blood flow

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The effect of epidural bupivacaine (5 mg/ml) on intestinal blood flow was studied with laser Doppler flowmetry in 15 patients during operations including various types of large bowel resection. In the colon, blood flow increased in 13 out of 15 patients, which was significant at the 1 per cent level. The average increase was 41 per cent. In the ileum an increase was found in eight out of eleven patients who could be studied, which was significant at the 5 per cent level. Bowel function was restored satisfactorily in all patients. It is concluded that epidural bupivacaine has a favourable effect on intestinal blood flow during colorectal surgery.

Keywords: Epidural anaesthesia, intestinal blood flow, laser Doppler flowmetry

The use of epidural anaesthesia during colorectal surgery decreases the need for intravenous analgesic drugs during operation and, with an epidural catheter, it is possible to give the patient good pain relief postoperatively without the use of opiates. Continuous or intermittent epidural administration of bupivacaine has been shown to shorten the postoperative intestinal paralysis by inhibition of different sympathetic reflex mechanisms[1], allowing earlier oral nutrition.

Anastomotic dehiscence is a serious complication after colorectal surgery, with incidences of 5–30 per cent being reported, and is associated with a high mortality[2–6]. One of the most important factors influencing the healing of the anastomosis is the microcirculation in the bowel wall involved in the anastomosis and attempts have been made to improve this factor[6].

Laser Doppler flowmetry (LDF) has, during recent years, been shown to be a useful technique for the study of intestinal microcirculation. In this application, it has been possible to calibrate the LD-signal in absolute flow units and, for the instrument used in this study, there is substantial evidence indicating a measuring depth of at least 6 mm when applied to the gastrointestinal wall, i.e. comprising the entire wall thickness of human small and large intestine[7–10].

LDF allows continuous measurement of intestinal blood flow and, contrary to most other methods available, it is convenient to use during routine operations[8–10].

The aim of this study was to investigate the effect of epidural bupivacaine on intestinal microcirculation during surgery, including large bowel resections.

Patients and methods

Fifteen unselected patients (*Table 1*) who had a large bowel resection were studied. Before general anaesthesia, an epidural catheter (diameter 1 mm) was introduced at an appropriate level (*Table 2*) and inserted 3–5 cm into the epidural space. After induction with thiopentone and suxamethonium, the patient was intubated and anaesthesia was maintained with nitrous oxide in oxygen supplemented with diazepam and fentanyl. Muscle relaxants (alcuronium or pancuronium) were given although they were usually not necessary after bupivacaine had been injected epidurally. The patients were ventilated with an Engstrom ventilator (2011) To ensure normocarbia, arterial P_{CO_2} was measured intermittently and end-tidal P_{CO_2} concentration was monitored continuously (Multicap, Datex) Blood pressure was measured automatically in the left upper arm with a sphygmomanometer (BP103N Mark III, Nippon Colin Co Ltd, Japan).

No drugs were given through the epidural catheter before the resection was completed The volumes of bupivacaine (5 mg/ml) given are listed in *Table 2*. The extent of the epidural analgesia was not determined during operation. A decrease in systemic blood pressure was taken as an indication of sympathetic nerve block No adrenergic drugs were given to treat the reduction in blood pressure.

The epidural catheter was used for postoperative analgesia. A lower concentration of bupivacaine (2·5 mg/ml) was used for this purpose and administered through the epidural catheter as a continuous infusion or by intermittent injection. The analgesic effect was evaluated subjectively on awake patients and according to their need of intravenous analgesic drugs.

Laser Doppler flowmetry

The operating principle of laser Doppler flowmetry with a differential detector system has been described in detail previously[12–13]. In this study, a laser Doppler system (Periflux®, PF2, serial No. 401, gain setting 10, time constant 3, frequency limit 12 kHz, Perimed, Stockholm, Sweden) was used, which has proved capable of monitoring blood flow changes even during vasodilatation[10]. Recordings were performed using a standard probe (Perimed, fibre diameter 0·7 mm, fibre centre separation 0·7 mm). The probe was inserted into a probe holder which eliminated the contact pressure at the site of measurement by keeping the probe at a distance of 0·6 mm from the tissue surface The probe holder, including the probe, was held manually against the intestinal wall. The probe was sterilized in 2 per cent glutaraldehyde (Cidex) before operation.

Blood flow measurements were performed after completion of the bowel resection, immediately before, and intermittently for 30 min after the injection of bupivacaine (5 mg/ml) in the epidural catheter

If an anastomosis had been constructed, flow measurements were performed, if possible, on both the proximal and distal margins of the anastomosis. In some cases with pelvic anastomoses it was not possible to record distal to the anastomosis In some, flow measurements were also performed on available segments of ileum and colon not involved in the anastomosis. The sites of measurement in each patient are listed in *Table 1*

Statistics

At each site of measurement, 2–5 flowmeter recordings were performed during each recording period and the average flowmeter signal level was used for analysis. The average laser Doppler signal level during 15–30 s was defined as one measurement Recording periods complicated by artefacts were excluded before data analysis. The number of patients is denoted by *n* Values are given as mean ±s.d. The Wilcoxon signed rank-sum test for paired samples was used for comparison of flowmeter signal levels before and after injection of bupivacaine in the epidural catheter

Results

In the colon, the flowmeter signal level increased in 13 of 15 patients after administration of bupivacaine in the epidural catheter (*Figure 1*). The average signal level of all patients increased from 17·4 ± 6·0 to 24·7 ± 10·3 V after administration of bupivacaine. The average increase in signal level was 41 per cent. The difference in signal levels is significant ($P < 0{\cdot}01$).

When an increase in signal level occurred it was usually apparent within 5–10 min of the administration of bupivacaine, as illustrated in *Figure 2*. Even the signal levels recorded 20–30 min after injection of epidural bupivacaine were significantly different ($P < 0{\cdot}01$) from the signal levels before the injection.

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Table 1 *Age, sex, diagnosis, operative procedure and the sites of laser Doppler flowmeter recording in each patient*

Patient no.	Age	Sex	Diagnosis	Operative procedure	Site of recording
1	85	F	Carcinoma of transverse colon	Resection of transverse colon	Descending colon (a)
2	67	F	Caecal carcinoma	Right hemicolectomy	Ileum (a) Transverse colon (a)
3	84	F	Caecal carcinoma	Right hemicolectomy	Ileum (a) Transverse colon (a)
4	77	F	Caecal carcinoma	Right hemicolectomy	Ileum (a) Transverse colon (a)
5	47	M	Sigmoid carcinoma	Left hemicolectomy	Rectum (a)
6	71	M	Sigmoid carcinoma, diverticulitis	Left hemicolectomy	Descending colon (a) Rectum (a) Ileum
7	54	M	Crohn's disease	Ileocolic resection	Ascending colon (a) Sigmoid colon
8	70	F	Caecal carcinoma	Right hemicolectomy	Ileum (a) Transverse colon (a)
9	72	F	Rectal carcinoma	Rectal amputation + colostomy	Transverse colon
10	59	F	Rectal carcinoma	Low anterior resection	Ileum Caecum Sigmoid colon (a)
11	84	M	Caecal carcinoma	Right hemicolectomy	Ileum (a) Transverse colon (a)
12	43	F	Crohn's disease	Ileocolic resection	Ileum (a) Ascending colon (a)
13	66	F	Rectal prolapse	Sigmoid resection Proctopexy	Ileum Caecum Rectum (a)
14	38	M	Rectal carcinoma	Low anterior resection	Descending colon (a) Ileum
15	75	F	Rectal carcinoma	High anterior resection	Descending colon (a) Ileum

(a), site of recording near the anastomosis

Table 2 *Level of insertion of the epidural catheter and volume of bupivacaine given in each patient*

Patient no	Level of epidural catheter	Volume of bupivacaine given (ml)	Systolic blood pressure (mmHg) Before	After	Postoperative analgesic effect	Increased small bowel motility (+)
1	Th_{12}-L_1	15	150	80	Good	+
2	L_1-L_2	13	130	75	Good	−
3	Th_{9-10}	8	140	100	Poor	−
4	Th_{8-9}	14	160	90	Good	+
5	Th_{9-10}	15	130	70	Good	+
6	L_{3-4}	15	160	100	Good	−
7	Th_{10-11}	13	170	130	Good	+
8	Th_{9-10}	12	180	110	Good	−
9	Th_{6-8}	9	168	80	Good	+
10	Th_{10-11}	13	150	90	Good	+
11	Th_{10-11}	11	140	140	None	−
12	Th_{12}–L_1	15	140	110	Poor	+
13	Th_{10-11}	10	170	140	Good	+
14	L_1–L_2	16	130	110	Good	+
15	L_1–L_2	13	130	115	Good	+

Change in systolic blood pressure after epidural bupivacaine administration, evaluation of postoperable analgesic effect and increase in small bowel motility, if any, are shown

There was no significant difference in the increase of the flowmeter signal levels between measuring sites on the left ($n = 10$) or right ($n = 9$) colon.

The systolic blood pressure decreased in all patients except one (No. 11) after administration of bupivacaine. In no case was the systolic blood pressure less than 70 mmHg. The changes in systolic blood pressure for each patient are listed in *Table 2*.

The analgesic effect of bupivacaine (2·5 mg/ml) post-operatively was good in all patients except Nos. 3, 11 and 12 (*Table 2*). In patients 3 and 12 the analgesic effect was poor and patient 11 experienced no effect at all on abdominal pain, sensory or motor functions.

In 10/15 patients there was an obvious visible increase in small bowel motility after administration of bupivacaine (*Table 2*). There was no obvious visible effect on colonic motility in any patient.

The increase in small bowel peristalsis after administration of bupivacaine disturbed the flowmeter recordings in some cases and made comparison of signal levels impossible. Despite this problem, comparable flowmeter signal levels from the ileum could be obtained in 11 out of 15 patients. The signal level increased in eight patients and the average signal level of all eleven patients increased from 16·9 ± 4·9 to 19·8 ± 8·4 V (*Figure 3*). The average increase in flowmeter signal level was

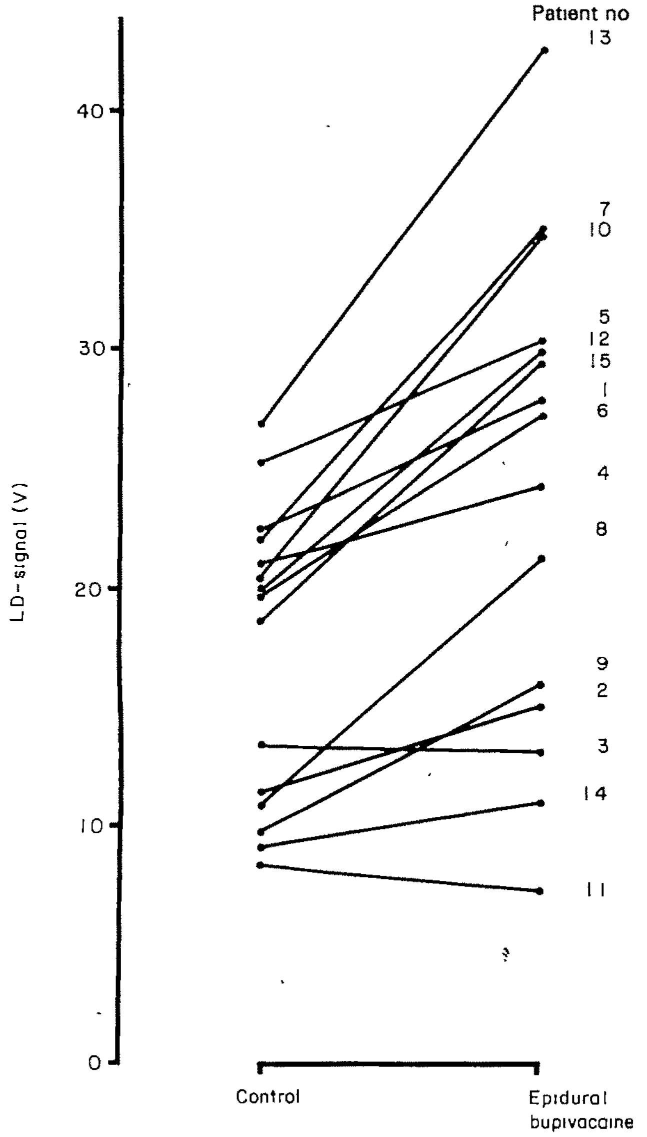

Figure 1 *Average laser Doppler flowmeter signal level obtained in the colon of each patient immediately before and at 5–30 min after administration of bupivacaine through the epidural catheter*

15 per cent. The difference in signal levels is significant at the 5 per cent level.

All patients recovered without complications that could be ascribed to the epidural anaesthesia or to anastomotic dehiscence, and were discharged from the hospital with satisfactory bowel function. A total number of 542 flowmeter recordings was made in the study: 54 of these (10 per cent) were unstable or complicated by artefacts (mostly movement artefacts).

Discussion

Healing of the anastomosis is probably the single most important factor in the results of colorectal surgery[2–6]. Several factors such as surgical technique, intra-operative faecal contamination, blood loss, nutritional state of the patient and the level of the resection have been shown to influence the incidence of anastomotic leakage[3–6].

Anaesthetic techniques used during and after colorectal surgery may influence anastomotic integrity and intestinal blood flow in different ways[2,14–17]. Although it is controversial, maintenance of an adequate haemoglobin concentration with optimal blood viscosity seems to be of importance[6], and experiments on dogs have shown a reduced colonic blood flow during hyperventilation and hypocapnia secondary to increased vascular resistance[16]. Adequate microcirculation of the bowel is clearly important for anastomotic healing, and dissection of the mesentery with manipulation of the bowel during operation can adversely effect mesenteric blood flow.

Our results clearly indicate that the administration of epidural bupivacaine significantly increases blood flow in the colon and probably also in the small intestine. The results of this clinical study are in accordance with the results obtained by Aitkenhead *et al.*[16], who found a 22 per cent increase in blood flow in the canine colon after subarachnoid spinal nerve block.

The extent of the neural blockade was not determined during operation, but the fall in systemic blood pressure and the adequate analgesic effect postoperatively in most patients clearly indicated sympathetic nerve blockade and a correctly positioned catheter. Patient 11 may, in this respect, serve as a control; in this patient, no change in intestinal blood flow or systemic blood pressure was seen and the effect of a further injection of bupivacaine postoperatively produced no signs of motor, sensory or sympathetic nerve blockade.

It is reasonable to believe that the effect on intestinal blood flow is due to a decreased mesenteric vascular resistance secondary to sympathetic nerve blockade, although a direct pharmacological effect from bupivacaine absorbed through epidural vessels cannot be excluded.

The variations in signal levels seen after the injection of epidural bupivacaine (*Figure 2*), might reflect a haemodynamic instability produced by changes in vascular resistance

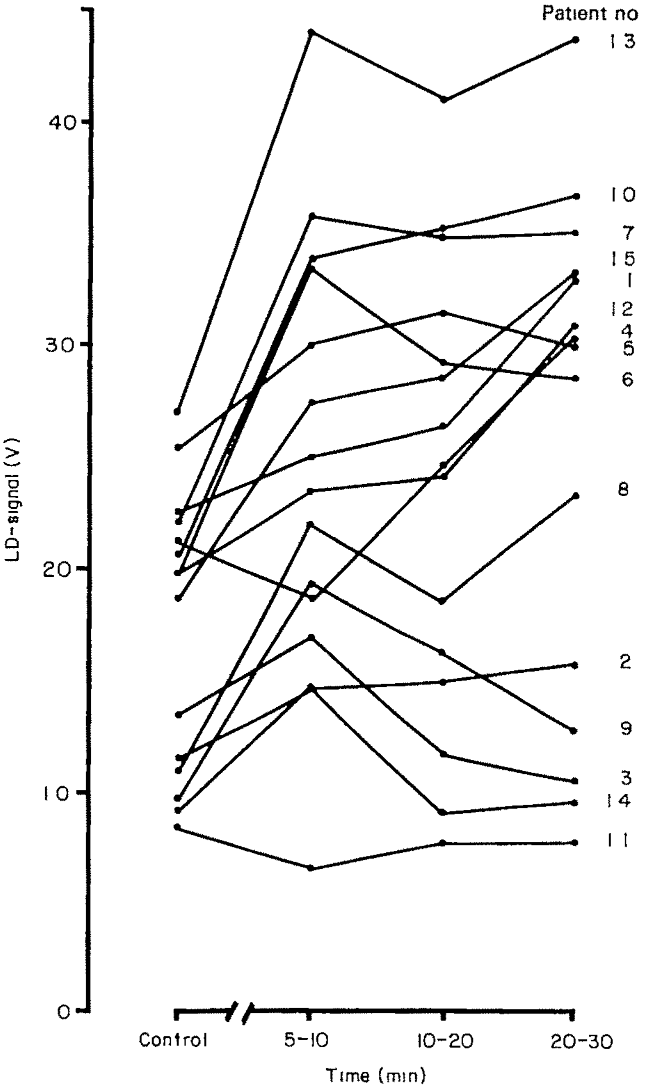

Figure 2 *Average laser Doppler signal level obtained in the colon of each patient immediately before and at three intervals after administration of bupivacaine through the epidural catheter*

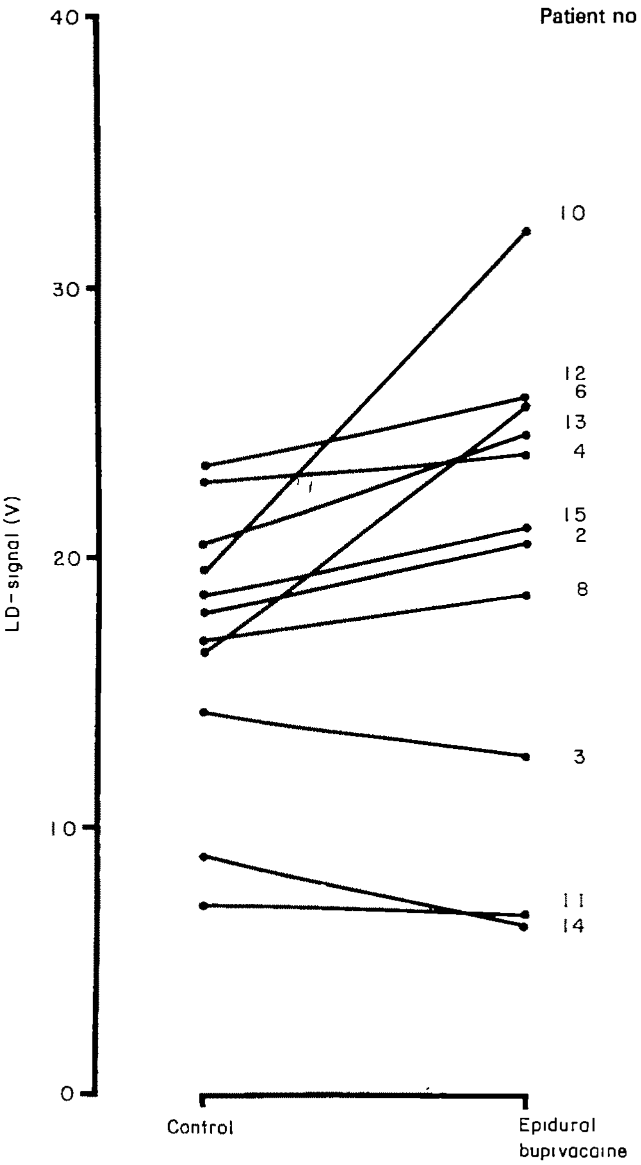

Figure 3 *Average laser Doppler flowmeter signal level obtained in the small intestine of each patient immediately before and at 5–30 min after administration of bupivacaine through the epidural catheter*

secondary to the sympathetic blockade.

The first 2–3 days after operation are considered the most critical for anastomotic integrity. In a study by Daos *et al.*[18], the effect of epidural anaesthesia was shown to be longer lasting on sympathetic functions than motor or sensory functions. Thus, if epidural local anaesthetics are used for postoperative analgesia with a remaining effect on intestinal blood flow, it should be favourable for healing of the anastomosis during this period, especially in those patients where microcirculation to the bowel involved in the anastomosis has been reduced due to surgical or haemodynamic factors.

Postoperative analgesia with epidural bupivacaine has also been shown to shorten the postoperative intestinal paralysis[1], but this form of postoperative analgesia remains a matter of debate as the increased motility has been claimed to increase the strain on the anastomosis and early disruption has been reported[19].

Another favourable effect of epidural anaesthesia during colorectal surgery is the reduced requirement for intravenous analgesics, neuromuscular blocking agents and, therefore, neostigmine at the end of surgery. Neostigmine has been shown to increase anastomotic dehiscence probably due to an excessive stimulation of motor activity in the bowel wall[20]. This study also showed that laser Doppler flowmetry is a useful method for clinical studies of intestinal microcirculation and that the method is convenient to apply during routine surgery. Motion artefacts remain the major disadvantage of the method. We conclude that epidural bupivacaine increases intestinal blood flow. This, together with other beneficial effects, makes it an attractive method of analgesia, both during and after colorectal surgery.

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Maximal isokinetic muscle strength in patients with primary hyperparathyroidism before and after parathyroid surgery

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*Primary hyperparathyroidism (HPT) is associated with symptoms of generalized fatigue and muscle weakness. The purpose of this study was to investigate muscular function in HPT quantitatively and to evaluate the effect of parathyroid surgery in this respect. The maximal isokinetic muscle strength (peak torque) of knee extension and flexion was measured with a Cybex-II dynamometer in 16 patients with primary HPT (mean serum calcium 2·81 ± 0·14 mmol/l), four of whom had subjective impairment of strength, and in nine control patients submitted to hemithyroidectomy due to atoxic thyroid adenoma. Before surgery there was no significant difference in muscle strength between the two groups, neither was there any consistent relationship between the subjective feeling of muscular weakness and the measured peak torque. Seven months after surgery the HPT patients had increased their muscle strength by 8 per cent (*P < 0·05*). The improvement was correlated with the pre-operative serum calcium levels (*r = 0·56, P = 0·02*) and was particularly seen in patients with pre-operative subjective muscular weakness. Patients with only slightly raised calcium values and without subjective muscular symptoms did not benefit clearly from surgery, compared with the controls. The study demonstrates that HPT patients, especially those with neuromuscular symptoms, can improve their muscle strength after parathyroid surgery.*

Keywords: Hyperparathyroidism, calcium, parathyroid hormone, muscle strength, parathyroid surgery

With the current practice of measuring serum calcium in a wide variety of indications, most patients with primary hyperparathyroidism (HPT) seem to be diagnosed fortuitously and have only a mild to moderate hypercalcaemia[1,2]. Many of them appear to be largely asymptomatic or present symptoms of generalized fatigue or psychiatric and neuromuscular disturbances[2–5]. The cause of these symptoms has not been established. In rare cases a severe proximal muscular weakness is present, which improves after parathyroid surgery[6–9]. Unspecific electromyographic changes and muscle fibre atrophy have been found in such patients[10]. Unselected HPT patients, on the other hand, have normal nerve conduction velocity and neuromuscular transmission[11] but have been reported to benefit from parathyroid surgery irrespective of pre-operative muscular complaints[12,13].

The aims of the study described here were to study the muscle function in HPT patients by quantitative measurements of the muscle strength, and to evaluate the effect of parathyroid surgery in patients with mild to moderate HPT. A major reason was to investigate if there was a clinically significant impairment of muscle force which had not been recognized by the patients themselves.

Patients and methods

The maximal isokinetic muscle strength (peak torque) was measured in 16 unselected patients with primary HPT (13 women and 3 men), and in 9 control patients (8 women and 1 man) who were admitted for hemithyroidectomy because of atoxic thyroid adenoma during the same period as that in which the HPT patients were investigated. The HPT patients were 26–76 years old with total serum calcium values from 2·61 to 3·05 mmol/l (mean 2·81 ± 0·14 (s.d.) mmol/l, normal range 2·20–2·60 mmol/l). The serum parathyroid hormone (PTH) concentrations were 0·68–1·57 arbitrary units/l (mean 1·14 ± 0·20 arbitrary units/l), measured by a radioimmunoassay method (normal range 0·40–1·08 arbitrary units/l)[14] Four of the sixteen patients described muscular weakness, five had general fatigue and seven no such complaints. The HPT patients as well as the control patients were clinically and biochemically euthyroid both before and after surgery. The control patients had normal serum calcium levels and, compared with the HPT patients, they were of similar age (53 ± 14 years in the controls and 58 ± 15 years in the HPT patients), height (167 ± 8 *versus* 164 ± 6 cm) and weight (71 ± 12 *versus* 71 ± 11 kg).

The muscle strength was measured 1–2 days before surgery for either HPT or thyroid disease and 4–10 months postoperatively (mean 7 ± 1·7 months) In the HPT patients surgery verified the diagnosis and at follow-up all patients were normocalcaemic.

Maximal voluntary isokinetic muscle strength (peak torque) of knee extension and flexion was measured in a Cybex-II dynamometer (Lumex Isokinetic Systems, Bay Shore, New York), with the patient in a sitting position. The device includes a temperature-compensated strain gauge transducer (Aeronautical Research Institute of Sweden) and an X/Y-recorder (Bryan 26700, High Speed). Muscle strength was recorded as peak torque output (*Figure 1*) as described earlier[15,16] and with a 4·8 per cent coefficient of variation[17]. Three maximal extensions and flexions were performed at an angular velocity of 30 degrees/s, with a resting period between each procedure The highest peak torque of extensions and flexions, respectively, was used for calculations.

Statistical methods

Paired *t* test and Wilcoxon signed rank test was applied when comparing pre- and postoperative results within the groups and unpaired *t*-test, as well as the Mann–Whitney *U* test, for comparison between the groups. Multiple regression analysis was used to correct values for interindividual differences in age, height and weight. A probability of < 0·05 was accepted as statistically significant.

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Results

There was a wide variation in values for the isokinetic muscle strength in both the HPT patients and the controls (*Figure 2*). Before surgery both the extension and flexion peak torques of the HPT patients were somewhat lower than those of the control group, but the differences were not statistically significant (*Table 1*). The four HPT patients with subjective complaints of muscular weakness were not distinguished by the pre-operative measurements (*Figure 2*).

In the HPT patients the pre-operative peak torque values correlated negatively with age (for extension $r = -0{\cdot}69$ $P < 0{\cdot}05$ and for flexion $r = -0{\cdot}62$, $P = 0{\cdot}01$) and positively with height (for extension $r = 0{\cdot}55$, $P < 0{\cdot}05$ and for flexion $r = 0{\cdot}54$, $P < 0{\cdot}05$) but not with weight. In the control patients there was also a negative correlation between the pre-operative peak torque for extension and age ($r = -0{\cdot}70$, $P < 0{\cdot}05$) but there were no correlations with height or weight.

At follow-up, some improvement in muscle strength was seen in both groups of patients (*Table 1* and *Figure 2*). In the HPT patients the mean peak torque increase was +7·5 per cent (−9 to +41 per cent, $P < 0{\cdot}05$) in extension and +9·2 per cent (−19 to +49 per cent, $P < 0{\cdot}05$) in flexion compared with +3·7 per cent (−5 to +26 per cent, $P > 0{\cdot}10$) and +3·2 per cent (−10 to +39 per cent, $P > 0{\cdot}10$), respectively, in the control group. The relative increase in muscular force was not significantly different between the groups. Three of the four HPT patients with pre-operative complaints of muscular weakness reported subjective improvement postoperatively, and they also displayed a clearly greater increase in muscle strength, +25 per cent in extension (+15 to +41 per cent) and +33 per cent in flexion (+11 to +49 per cent), compared with +3·5 per cent in extension and +3·7 per cent in flexion torque in the remaining 13 patients.

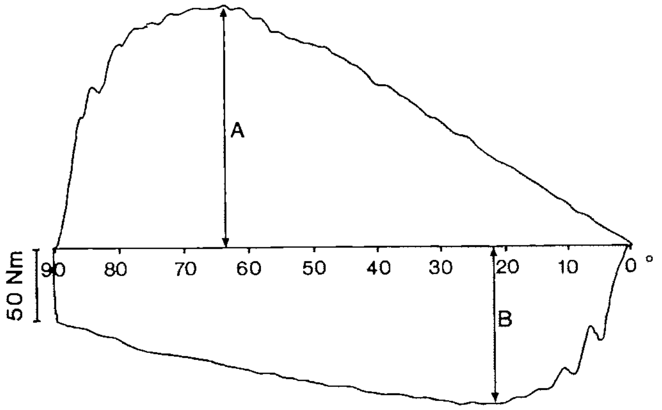

Figure 1 *Peak torque during one extension (A) and one flexion (B) of the knee, measured in a Cybex-II dynamometer. y axis shows the angle of knee flexion*

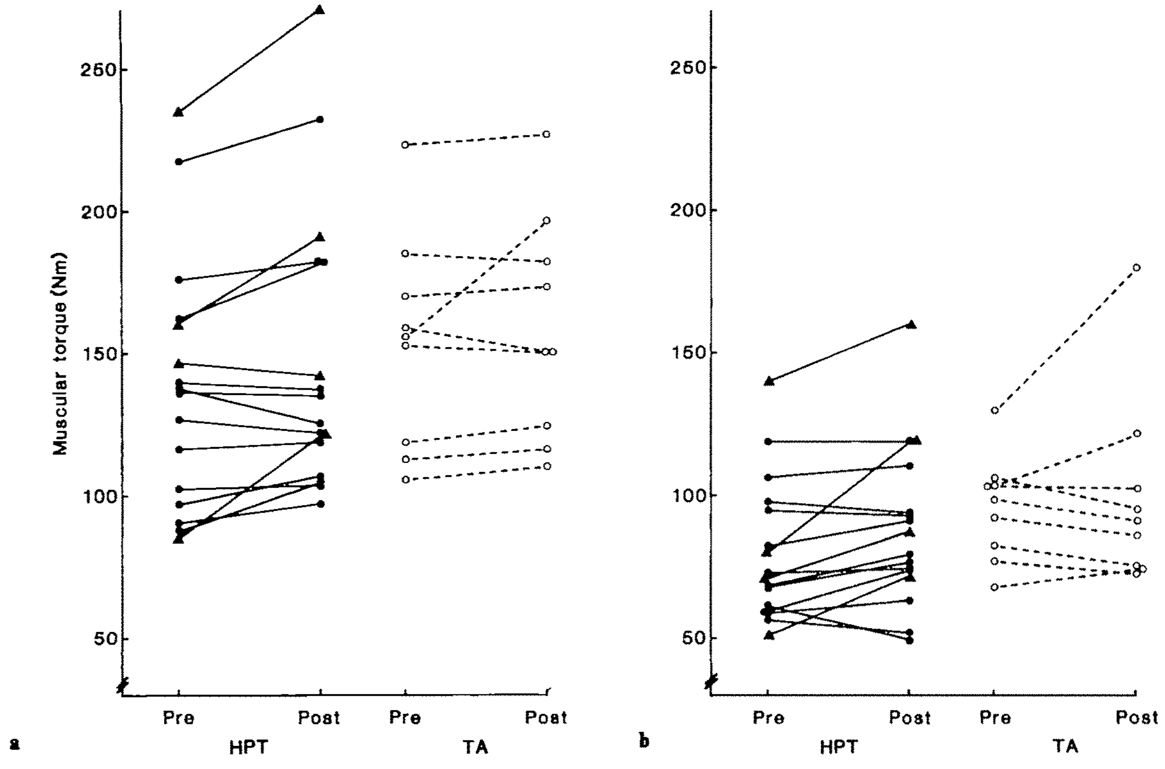

Figure 2 *Peak torque of* **a**, *knee extension and* **b**, *knee flexion, pre- and postoperatively in 16 HPT patients (———) and in 9 control patients with thyroid adenoma (TA) (– – –) HPT patients with (▲) and patients without (●) subjective muscle weakness*

Table 1 *Measurements of maximal isokinetic muscle strength pre-operatively, postoperatively and the relative change in percentage of pre-operative values (percentage change) for knee extension and flexion in 16 HPT patients and 9 control patients*

	Extension			Flexion		
	Pre-op. (Nm)	Postop. (Nm)	Percentage change	Pre-op. (Nm)	Postop. (Nm)	Percentage change
HPT	139±44	148±50*	7·5±12*	81±26	88±29*	9·2±17*
Control	154±38	159±39	3·7± 9	96±18	100±34	3·2±16

Values are mean±s.d.

* $P < 0{\cdot}05$ for the change from pre-operative to postoperative values

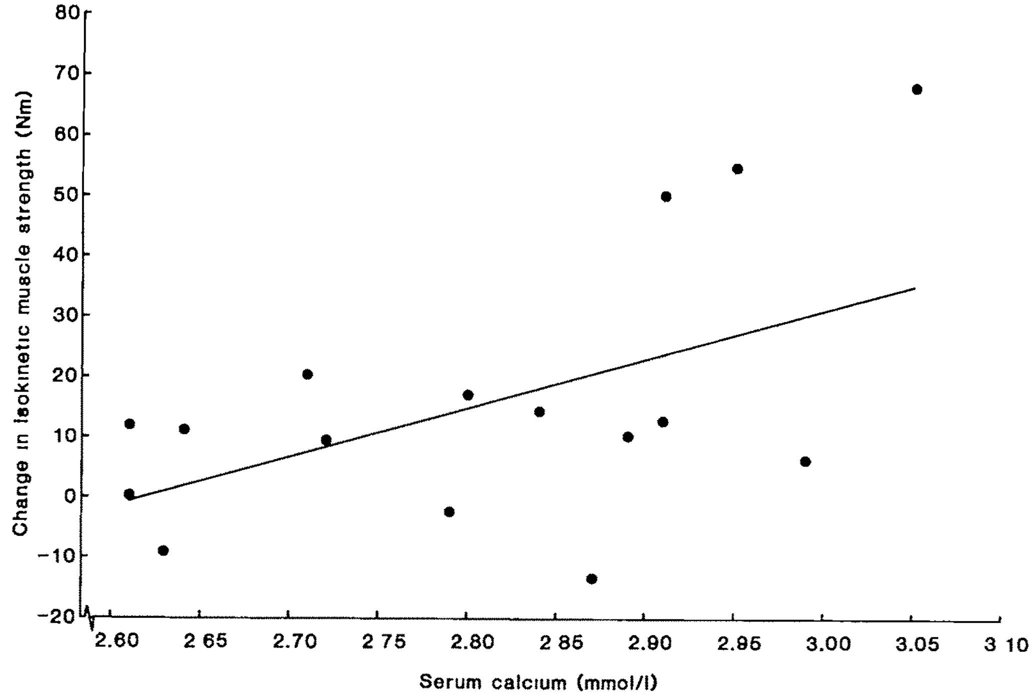

Figure 3 *Pre-operative serum calcium levels (mmol/l) and postoperative changes in absolute values of muscle strength ((extension+flexion), Nm) of the 16 patients operated upon for HPT.* $r=0{\cdot}56$, $P<0{\cdot}05$

In the HPT patients the pre-operative muscle strength was correlated neither with serum calcium nor with PTH concentrations. The absolute improvement of muscle strength was, however, correlated with the pre-operative serum calcium levels (for (extension+flexion) $r=0{\cdot}56$, $P=0{\cdot}02$), and a clear improvement was only seen in those with marked pre-operative hypercalcaemia (*Figure 3*). This relationship persisted ($P<0{\cdot}03$) in the multiple regression analysis when PTH, age and height were taken into account. There was no correlation between the improvement in muscle strength and pre-operative PTH levels.

Discussion

Many HPT patients complain of general or muscular fatigue but severe muscular weakness is seen only occasionally[6–9]. Minor degrees of muscular dysfunction are not readily identified in HPT. In a previous study[11] where we examined nerve function and neuromuscular transmission with the use of elaborate techniques, including the single fibre electromyography (EMG) method, we could not detect other than slight subclinical disturbances in a small fraction of consecutive patients with primary HPT. A main objective in the present investigation was therefore to analyse unselected HPT patients with mild to moderate hypercalcaemia for objective signs of muscular impairment, reversible by parathyroid surgery, and, if so, to use the muscular function test in the pre-operative assessment of especially the apparently 'asymptomatic' patient with HPT.

Our study demonstrated, however, that HPT patients who had no apparent subjective symptoms did not generally have any clinically significant impairment of muscle force. Thus before surgery they only had an insignificantly lower muscle peak torque than the control patients and they displayed only a slight postoperative improvement. The isokinetic muscle torque method is dependent on the patient's co-operation and therefore is not completely objective. The HPT patients often have mental depression and fatiguability[5] which could impair their voluntary effort and thus their test results. However, as far as could be judged, the exertion appeared to be similar in the two patient groups.

The calcium ion has a central role in muscle function and it is conceivable that alterations of calcium homeostasis can affect muscle strength. Furthermore, excess of PTH by itself appears to have detrimental effects on skeletal muscle metabolism[18,19]. No direct correlations have been demonstrated earlier in HPT between the serum calcium or PTH levels, on the one hand, and the degree of muscular dysfunction, on the other[8,20]. However, in the study described here, which obtained a quantitative measure, we found that the improvement (but not the pre-operative values) in the muscle strength was correlated with the degree of hypercalcaemia. The patients with clear muscle strength improvement had marked hypercalcaemia and pre-operative muscular symptoms, whereas patients with mild hypercalcaemia and without subjective muscle symptoms improved less after surgery. In the control group the slight postoperative improvement was mainly confined to two individuals. Though these patients were biochemically euthyroid they may have had some subclinical dysfunction, possibly influencing the muscle function pre-operatively. The difficulties in finding an appropriate, surgical, control group to the HPT patients are obvious.

There was no correlation between the subjective symptoms of muscle weakness and the peak torque values. One possible explanation is that there was a wide range of these values in the HPT patients and that the feeling of muscular weakness may be related to the individual decrease in muscle force rather than to the absolute force *per se*. It should also be noted that most of our HPT patients had comparatively mild hypercalcaemia (only one patient had a value above 3 mmol/l), i.e. there was little separation with regard to serum calcium values This may explain the absence of a statistical relationship between the serum calcium or PTH levels and the recorded muscle force except for the marked improvement after operation in those with the most pronounced hypercalcaemia.

Our investigation corroborates and extends the findings of other recent studies[12,13]. However, Hedman *et al.*[12] reported on strength improvement in maximal isokinetic knee extension and flexion only at 120 degrees/s or more, in asymptomatic HPT patients, while Wersäll-Robertson *et al.*[13] demonstrated a greater benefit from surgery at 30 degrees/s, i.e. the same as that utilized in the present investigation. Together with this study, these investigations indicate that there is an impairment of the muscle force in patients with HPT, which is reversible by parathyroid surgery. Our results demonstrate that HPT patients with subjective muscular symptoms—especially those with higher serum calcium values—benefit, in muscle function, from parathyroid surgery whereas those without such symptoms do not markedly improve in this respect after parathyroid surgery.

Together with our earlier experience from studies of the nerve function and the neuromuscular transmission[11], the present findings suggest that the cause for the muscle weakness in HPT seems to reside in the muscle itself. However, at least a part of the patient's subjective feelings of weakness and general fatigue cannot be revealed by muscle force measurements and may be of central nervous origin[5].

Acknowledgements

We thank Jan Hall for technical assistance. This study was supported by grants from Fredrik and Ingrid Thurings Foundation and from the Swedish Medical Research Council.

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Platelet aggregation on peritoneal tube grafts and double velour grafts in the inferior vena cava of the pig

In 14 pigs the infrarenal vena cava was replaced with a peritoneal tube graft or a collagen-coated double velour graft. With ^{111}In-labelled platelets dynamic in vivo *imaging of platelet aggregation over the graft was carried out using a scintillation camera. After removal, the grafts were examined by autoradiography for an evaluation of the platelet aggregation pattern. Measurements of activity in different regions of the grafts were also performed. The results indicated low activity uptakes both* in vivo *and* in vitro. *The dynamic study did not show any uniform increase of activity content 1–3 h postoperatively, in any of the groups. During the period 2–3 h postoperatively no increasing activity accumulation was found. Hemashield® Microvel® grafts had an uptake of 0·19 per cent of the total activity while the corresponding figure for peritoneal tube grafts was 0·17 per cent. The activity distribution on different parts of the grafts indicated lower accumulation on the Hemashield graft surfaces than in the anastomoses, while the accumulation was higher on the graft surface of peritoneal tube grafts. The autoradiographical findings supported this indication. In conclusion, low platelet aggregation was found with both dynamic* in vivo *imaging and* in vitro *activity measurements on both peritoneal tube grafts and collagen-coated double velour grafts.*

Keywords: Peritoneum, Dacron, inferior vena cava, platelets, indium, vascular surgery

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Venous grafting procedures imply a challenge in vascular surgery. Patency rates with grafts in the venous system are commonly less satisfactory than in the arterial system[1], mainly due to the low non-pulsatile flow velocity and the low pressure in veins. Grafting of the inferior vena cava may be necessary in cases of trauma or major tumour surgery involving the vena cava. Several types of grafts have been evaluated and, so far, results with autologous vein grafts are superior. However, the lack of suitable veins for grafting of larger veins, e.g. the vena cava, makes the search for alternative graft materials necessary.

Early graft failure is assumed to be caused by thrombosis because all grafts are more or less thrombogenic and platelets are activated and aggregated on non-endothelial surfaces[2]. So far, we do not know of any non-thrombogenic vascular surface material, except the uninjured endothelium.

To study platelet aggregation on grafts, platelet-labelling with ^{111}In has been used in dynamic studies[3,4].

In arterial grafts, there usually seems to be increasing activity over the graft during the initial postoperative hours[5]. Studies of platelet aggregation on grafts in the canine venous system have been presented by Plate *et al.*[6] who found that 3 h postoperatively the main aggregation had occurred on the cranial anastomosis and on the graft surface of PTFE-grafts in the inferior vena cava. Studies of platelet aggregation on grafts in the venous system through dynamic imaging have not, however, been presented.

The aim of this study was to evaluate platelet aggregation on peritoneal tube grafts. For comparison a collagen-coated double velour graft was used. ^{111}In-oxine labelled platelets were used for both dynamic *in vivo* imaging and for *in vitro* measurements of activity accumulation.

Materials and methods

The experimental design is shown in *Figure 1* Fourteen Swedish domestic pigs, weighing about 20 kg, were used for the experiments. They were anaesthetized with intravenous thiopentalum (Pentothal®, Abbot, Sweden), after which they were intubated and ventilated with nitrous oxide and oxygen, using a mechanical ventilator (Siemens-Elema, Sweden). Anaesthesia was maintained with infusion of ketaminum (Ketalar®, Parke-Davis, USA) in glucose solution. Before surgery one catheter was placed in the jugular vein for withdrawal of blood and for infusion Another catheter was inserted into the carotid artery for blood gas analysis and ventilation was adjusted when necessary

Labelling procedure

Before surgery, 120 ml of blood was carefully withdrawn for platelet labelling with approximately 20 MBq of ^{111}In-oxine, according to a method described by Thörne *et al.*[7] after modification by Hardeman[8]. For determination of labelling efficiency, small samples (50 µl × 2) of the platelet suspension were centrifuged in a haematocrit tube and the activity of the cells was compared with that of the supernatant. During surgery, shortly before declamping (see below) the labelled platelets were re-infused into the animal.

Operative procedure

Through a midline laparotomy, the intestines were reflected to the left and kept moist with a gauze swab. The inferior vena cava distal to the renal veins was dissected free After clamping below the renal veins and above the confluence of the iliac veins, the midportion of the vena cava was excised and replaced with one of the two grafts to be studied.

In seven animals, peritoneum below the xiphoid process was carefully dissected from the abdominal wall, cleaned from fat and excised. A tube was constructed with a plastic syringe (11 mm diameter) as a stent, using interrupted, everting 6-0 polypropylene (Prolene®,

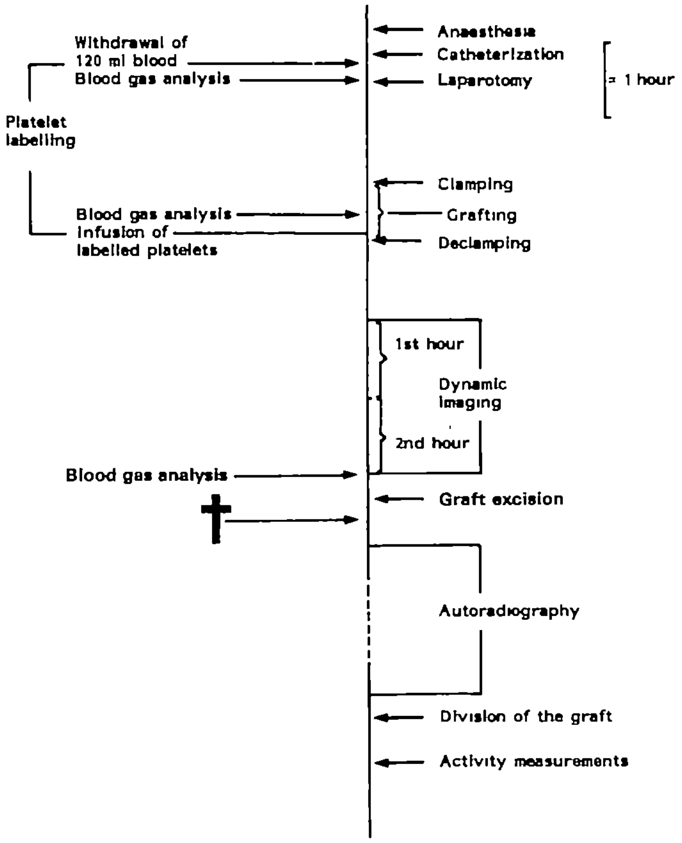

Figure 1 *The experimental design*

Ethicon) sutures. The inner surface of the peritoneum served as the luminal surface of the tube graft. The graft, about 2 cm long, was anastomosed end-to-end to the vena cava with 6-0 Prolene sutures. The posterior part of the anastomosis was sewn with continuous everting sutures and the anterior part with interrupted everting sutures. Care was taken to avoid any fat in the anastomoses

In seven animals a Dacron® (C. R. Bard Inc., Massachusetts, USA) double velour graft, 10 mm in diameter and 2 cm long, impregnated with collagen (Microvel® Hemashield®, Meadox Medicals Inc, USA) was used as an interposition graft. End-to-end anastomoses were performed with continuous 6-0 Prolene sutures with everted vein walls

The labelled platelets were now re-infused and, after declamping, haemostasis was controlled with gentle pressure with a swab. The anastomoses were carried out using 2·5 times optical magnification. The vein ends and the grafts were rinsed with heparinized saline, but no systemic heparinization was used. After adequate haemostasis the wound was closed.

Scintillation camera technique

After surgery the animal was placed in a supine position under a scintillation camera in a specially moulded plastic stand to secure an unchanged position. The scintillation camera (Maxi-camera®, General Electric, USA) was equipped with a medium energy parallel hole collimator. An energy window of 25 per cent was centred over the 245 keV full-energy peak of ^{111}In.

The activity uptake over the abdomen was continuously registered for 120 min, starting 1 h after release of the vascular clamps, with sequential 2 min images which were stored in a computer (Gamma 11, Digital Equipment, Massachusetts, USA) Regions of interest were selected in the image over the graft and over the native vena cava cranial to the graft (*Figure 2*). Time–activity curves were generated and the quotient between the count rates of the ROIg and ROIv were calculated. This quotient represented the platelet aggregation over the graft.

Activity measurements in vitro *and autoradiography*

After the scintillation camera measurement, the graft with the adjacent vein was excised. For autoradiography, the graft was gently rinsed in saline and placed between two plastic foils, transferred to an ordinary X-ray film in close contact and placed in a light-proof cassette. The film was exposed for 7 h after which it was developed giving the distribution of the ^{111}In-labelled platelets on the graft surface.

To measure the distribution of adhered ^{111}In-platelets quantitatively, the graft was, after autoradiography, carefully cut transversely into sections 5 mm long and transferred to test tubes The count rate was then measured in a NaI(Tl)-well counter. The platelet adhesion on the graft, as a percentage of injected labelled platelets, could then be calculated according to the formula·

$$\text{Platelet adhesion} = \frac{N}{k \times \varepsilon \times A} \times 100\,(\%)$$

where

N = the count rate, i.e. counts per second (CPS)

k = a calibration constant for the NaI(Tl)-detector used (CPS/MBq)

ε = the labelling efficiency

A = the injected activity (MBq)

Statistical analysis

In the dynamic study the time-frame was equalized, in the sense that measurements were performed under the same biological conditions The time-series, thus created, were homogeneous in variability over time, and so the prerequisites for estimation with least-square techniques were fulfilled and estimation of slopes in the regression lines and coefficient of determinations could be calculated and analysed.

For the statistical analysis of the *in vitro* measurements it was necessary to use non-parametric techniques because of the small samples from an unknown distribution.

The Mann–Whitney test was used for the analysis between the two different grafts and for comparison within the same graft the Wilcoxon signed rank test was used The term statistical significance means $P < 0.05$

Results

All the animals survived the experimental procedure. The clamping time did not differ between the Hemashield group and the peritoneal tube group.

All the grafts were patent at the end of the experiment. In all cases the inner surface was covered with a glistening thin red layer. However, in one peritoneal tube graft a large, non-occluding thrombus, attached to the cranial anastomosis, was also found. This was probably caused by a piece of fat, found in the cranial anastomosis, representing a technical failure.

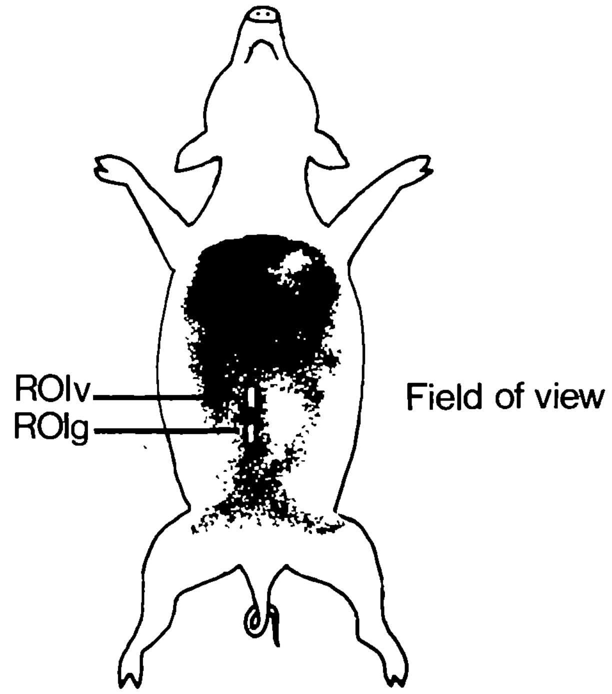

Figure 2 *A picture from the dynamic imaging of a peritoneal tube graft. Regions of interest over the graft (ROIg) and over the native vein cranial to the grafts (ROIv) are selected*

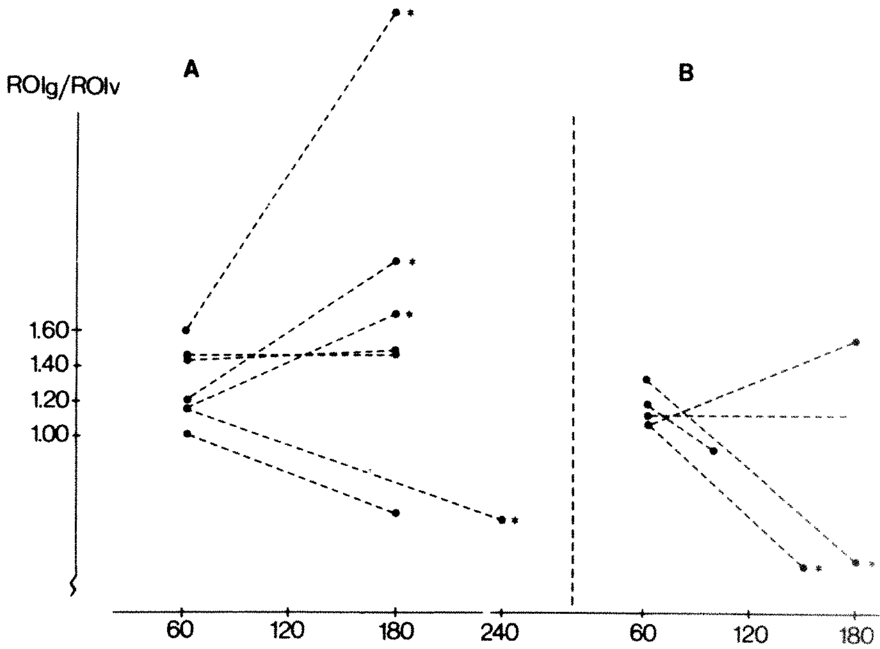

Figure 3 *Time–activity curves, transformed to regression lines during 1–3 h after declamping. A, peritoneal tube grafts; B, Hemashield grafts. The initial points of the curves represent the initial ratio between the regions of interest over the graft (ROIg) and over the native vein cranial to the graft (ROIv). *Significant increase or decrease,* $P<0·05$

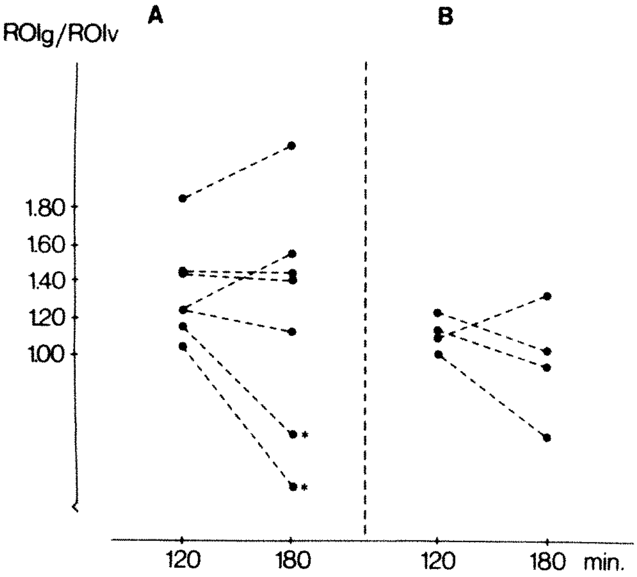

Figure 4 *Time–activity curves transformed to regression lines during 2–3 h after declamping. A, peritoneal tube grafts; B, Hemashield grafts. The initial points of the curves represent the ratio between regions of interest over the graft (ROIg) and over the native vein cranial to the graft (ROIv) at 120 min after declamping. *Significant decrease,* $P<0·05$

The labelling efficiency did not differ between the groups (median 59 per cent (range 55–66) and median 56 per cent (range 52–67), respectively).

Scintillation camera study

From the dynamic studies, it was possible to generate curves for 12 animals (5 Hemashield grafts, 7 peritoneal tube grafts). In two experiments, due to technical failure in the measurements, it was not possible to secure adequate ROI for measurements.

The time–activity curves showed a significantly decreasing activity content in two Hemashield and in one peritoneal tube graft. In one Hemashield graft and three peritoneal tube grafts, however, the activity accumulation increased significantly (*Figure 3*). One of the latter was generated from the graft with the large thrombus. In the remaining curves (two Hemashield grafts, three peritoneal tube grafts) the accumulation did not significantly change. For further evaluation of the dynamic course, the time–activity curves were evaluated separately during only the second hour of imaging (*Figure 4*); in no instance did these reveal any significantly increased uptake. However, in two cases (peritoneal tube grafts) significantly decreasing activity contents were found. In all the others the dynamic course was mainly unchanged during this second hour of imaging. The graft with the thrombus did not show any significantly increased activity accumulation during this period.

In vitro *measurements*

In vitro activity measurements were not performed in the first two experiments. Measurements were obtained in only 12 grafts (7 Hemashield grafts, 5 peritoneal tube grafts) (*Figure 5*). The activity on the surface of the graft with the thrombus was about four times as high as that of the other grafts (0·74 per cent). The activity, measured over the entire surface of the other grafts, did not vary between the two groups (median 0·19 per cent (range 0·03–0·32) and 0·17 per cent (range 0·09–0·39)). The activity over the different parts of the graft surfaces, excluding the anastomoses, did not differ significantly. The mean values of the intermediate graft surfaces are compared with those of the cranial and caudal anastomoses. Between the groups the amount of activity in the different parts of the grafts did not reach a statistically significant difference. There was, however, an impression that the pattern of activity was different, in that the Hemashield grafts had generally a larger activity accumulation in the anastomotic regions than on the intermediate graft surfaces, while the opposite was found on the peritoneal tube grafts.

Autoradiography

Autoradiographs were performed on 12 grafts (6 Hemashield grafts, 6 peritoneal tube grafts). They gave a visual image of the distribution pattern of platelet aggregation on the surface. All peritoneal tube grafts showed a fairly homogeneous film density, whereas the Hemashield grafts were more dense near the anastomoses than in the middle; in only two cases was the density of the Hemashield graft homogeneous. The peritoneal tube graft with the thrombus was extremely dense around the cranial anastomosis. Typical autoradiographs are shown in *Figure 6*.

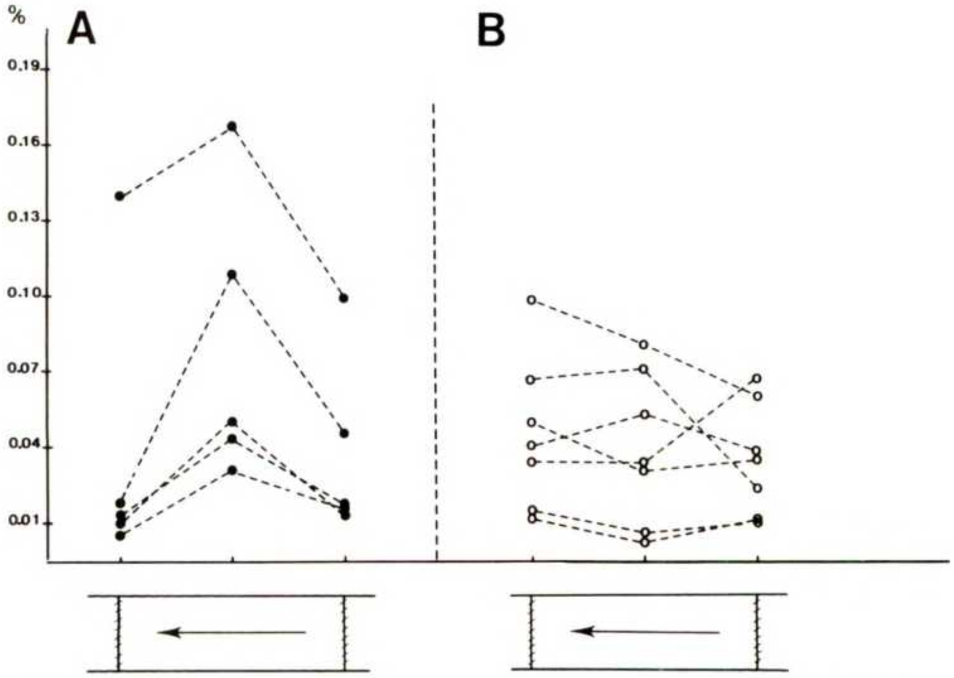

Figure 5 In vitro *activity measurements in the different parts of the grafts. A, peritoneal tube grafts; B, Hemashield grafts. Values are given as a percentage of infused labelled platelets. The mean values of the intermediate graft surfaces are compared with those of the cranial and caudal anastomoses. No statistically significant differences were found*

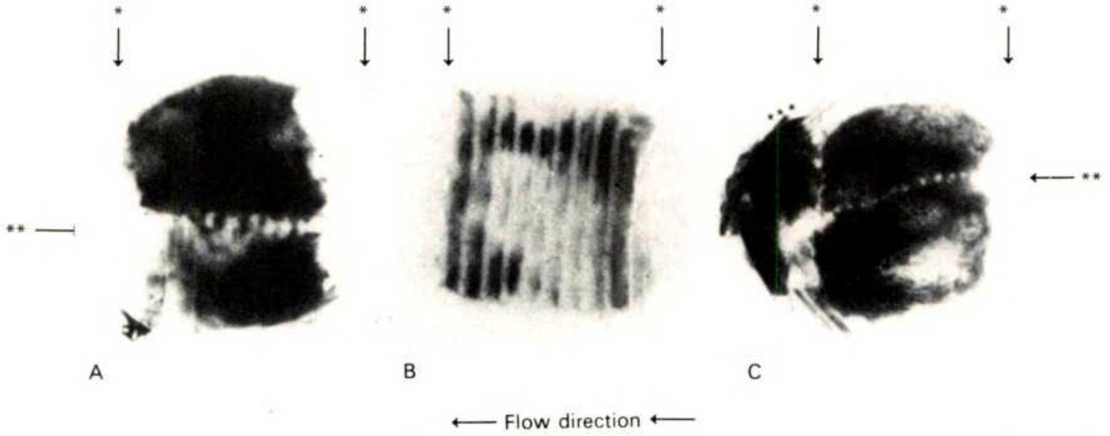

Figure 6 *Representative autoradiographs of A: peritoneal tube graft, B: Hemashield graft. C shows the peritoneal tube graft with the thrombus. Direction of flow (large arrow) is from right to left. *Anastomotic region; **longitudinal suture line; *** thrombus (C)*

Discussion

Repair or reconstruction of the inferior vena cava involves several problems such as lack of suitable graft material and a high incidence of thrombotic failures. Better results are usually achieved in the superior vena cava[9], which is probably due to the higher flow rate there than in the infrarenal vena cava. In a previous study in rats we achieved reasonable results with caval grafting with peritoneal tubes below the renal veins[10]. The aim of the present study was, therefore, to evaluate the same model in a larger animal. The choice of a collagen-coated graft for comparison was based on the assumption that such a material would carry a high risk of thrombotic occlusion in the venous system, as collagen is known to be a potent platelet aggregator. The results showed surprisingly small activity contents, indicating a low tendency for platelet aggregation on both the peritoneal tube grafts and the collagen-coated double velour grafts. With dynamic scintillation camera imaging 1–3 h postoperatively no specific pattern was found, which is in contrast to reports of imaging on prosthetic arterial grafts, generally showing a strong aggregation of platelets during the first 2–3 h postoperatively[11,12]. Some grafts in both our groups showed increasing activity accumulations, indicating aggregation, whereas others had a decreasing tendency, which may indicate release of platelets. During the second hour of imaging, i.e. 2–3 h postoperatively, it seemed as if a steady state was already achieved. No curves showed any significant increase during this period, whereas two curves decreased. This could be interpreted as release of platelet aggregates from the surface. Previously, this possibility has been discussed in studies of arterial grafts[11]. It must be borne in mind that all the dynamic examinations in our study were started 1 h after the release of blood flow. Any aggregation that may occur probably starts immediately after declamping, and our results indicate a variability in time when the graft surface is 'saturated'. On the other hand the labelled platelets were injected before release of blood flow. It is unlikely that an early aggregation could have been missed in the measurements.

From the *in vitro* activity measurements the aggregation of platelets did not differ between the peritoneal tube grafts and the Hemashield grafts. There was no significant difference in activity uptake in the different parts of the grafts as noted by Plate *et al.*[6], who reported the highest activity content over the cranial anastomosis of venous PTFE-grafts, followed by that of the intermediate graft surface and lowest activity in the caudal anastomosis. On the other hand, Gloviczki *et al.*[13] found the largest accumulation on the graft surface and smaller in the anastomotic regions. An explanation to this difference might be that the former authors used cranial end-to-end anastomoses, which implies the risk of turbulent flow, whereas Gloviczki *et al.* used end-to-end anastomoses. Although not statistically significant, we had the impression that our Hemashield grafts had larger activity accumulations in the anastomotic regions than on the graft surfaces, whereas the peritoneal tube grafts seemed to have the peak uptake on the graft surface. The findings of autoradiography strengthened this impression. The longitudinal suture row of peritoneal tube grafts is a potential source for platelet aggregation. The assumption that the collagen coating of the Hemashield grafts would cause augmented platelet aggregation was not realized. Recently, the thrombogenicity of this graft was evaluated in the canine aorta and it was in fact found to be less thrombogenic than non-coated double velour grafts[14]. It was thought that the activity of collagen was blocked by cross-linking during fabrication.

A meticulous technique is of tremendous importance in all vascular surgery. Turbulent flow and irregularities in anastomoses have to be avoided. In one graft in this study aggregation of platelets immediately occurred where fat had inadvertently been included in the anastomosis. The grafts were as isodiametric as possible (10–11 mm diameter) to avoid the risk of turbulent flow. The reconstructions were performed with two end-to-end anastomoses that also provide the best flow conditions. The eversion of the vessel ends also helps to provide a smooth anastomosis. Another factor that may contribute to the low aggregation of platelets in this study is the short length of the grafts. The two tested types of grafts represent one autologous and one prosthetic material. Autologous material has the advantage of non-antigenicity and, probably, a lower risk of infection. The peritoneum is readily available in large amounts, and its mesothelium resembles the endothelium in that it is found to have fibrinolytic[15,16] and prostacyclin[17,18] activity. These facts would theoretically make the material suitable as a graft. However, mesothelial cells are easily damaged and when perfusion through the graft is started the majority of mesothelial cells are injured, as seen in a few scanning electron-microscopical studies, performed by us. Louagie *et al.*[19] studied the fibrinolytic activity of peritoneal patch grafts and found an immediate reduction of activity which from the fourth day postoperatively, increased to higher values than that of the controls. The low values of platelet aggregation in our study might indicate that the graft surface is not as thrombogenic as would be expected, even if the mesothelial cells are injured. The compound prosthesis, Hemashield–Microvel, is a double velour graft where the surface is covered with bovine collagen. This has the clinical advantage, especially in emergency arterial surgery, that preclotting is unnecessary because the collagen makes the graft impermeable to blood[20]. Small grafts (4 mm diameter), experimentally used in the arterial position have, however, shown higher occlusion rates and higher uptake of platelets than non-coated double velour grafts[12].

In conclusion, this study has shown a low aggregation of platelets on both peritoneal tube grafts and collagen-coated double velour grafts in the infrarenal vena cava of the pig. This was found both by dynamic *in vivo* imaging in the direct postoperative period and by activity measurements *in vitro*.

The study supports the assumption that the readily available peritoneum can serve as a vascular graft, and it also indicates that the collagen-coated Hemashield graft has a low thrombogenicity. These findings must, however, be confirmed in long-term studies and longer grafts have to be examined.

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Small bowel volvulus complicating intestinal ascariasis in children

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Twenty-nine patients in whom small bowel volvulus complicated intestinal ascariasis are reported. Attention is drawn to the varied clinical and radiological presentation and the relationship of volvulus to the use of vermifuge. The mortality of 17 per cent was contributed to by delay in diagnosis and failure of pre-operative resuscitation. Early diagnosis is dependent upon clinical vigilance and repeated radiological assessment of those patients with simple ascaris obstruction who fail to improve rapidly with conservative treatment. The instillation of intraluminal vermifuge intra-operatively has minimized postoperative worm migration through suture lines and anastomoses.

Keywords: Ascariasis, volvulus

The roundworm *Ascaris lumbricoides* is the commonest intestinal parasite of man, and in tropical and subtropical areas where 90 per cent of the population are affected[1], represents a major health problem. The surgical complications of ascaris infestation are legion[2–5], yet relative to the asymptomatic carrier population, surprisingly uncommon. Children in endemic areas are at greater risk of massive infestation, both absolute and relative[1,2], most frequently presenting with subacute intestinal obstruction due to luminal occlusion by an inter-twined bolus of worms[6]. We report the history and clinical course of 29 patients in whom small bowel volvulus complicated intestinal ascariasis, in order to emphasize the importance of an awareness of this lesion and the varied clinical and radiological presentations.

Patients and methods

Twenty-nine consecutive patients presenting to this department from 1978 to 1986 with small bowel volvulus secondary to intestinal ascariasis were reviewed retrospectively. All patients in whom small bowel volvulus was confirmed at autopsy or operation, with a mass of worms present in the volved segment and no other cause of volvulus evident, were included in the review (*Figure 1*). These patients represented approximately 1 per cent of the total surgical admissions for sequelae of ascariasis and 10 per cent of operations performed for such sequelae during the review period. The patients' ages ranged from 9 months to 10 years (mean 4 years). Females predominated by 1·7:1.

Clinical presentation

In 17 patients (59 per cent) the need for emergency surgery was evident at presentation. Five of these children had advanced peritonitis and were critically ill. A further ten children had signs and symptoms of acute intestinal obstruction with abdominal tenderness, and in a further two children a clinical assessment of incomplete or subacute bolus obstruction was belied by radiographic findings typical of volvulus. Of these 17 children, 10 (59 per cent) had passed worms *per oram* or *per rectum* and vermifuge had been administered to 8 (47 per cent) before surgical presentation.

Twelve patients (41 per cent) had no compelling features at presentation. Nine (75 per cent) of this group were vomiting worms or passing worms in stool. Three (25 per cent) had been treated with vermifuge before referral. Two patients had radiological signs of volvulus which initially were misinterpreted, and conservative management was initiated.

Radiological evaluation

In nine children (31 per cent) plain abdominal radiographs on admission demonstrated the characteristic features of a small bowel volvulus, the 'target sign': this is a closed loop obstruction formed by the concentric loops of distended bowel containing worms, surrounding a relatively radio-opaque mesentery. In a further nine children (31 per cent) complete, and in six (21 per cent) incomplete, intestinal obstruction was diagnosed. In five children (17 per cent) a worm bolus was radiologically evident without obstructive features. Thus, in 69 per cent of patients, subsequently demonstrated to have enteric volvulus, either radiology on admission failed to reveal typical features, or the volvulus developed upon bolus obstruction during conservative management.

Haematological and biochemical investigation, although providing essential baselines for perioperative management, had no diagnostic significance.

Management

Seventeen patients requiring urgent surgery were resuscitated before operation. Pre-operative antibiotics were prescribed and intravenous crystalloids and plasma administered, with the aim of producing adequate peripheral perfusion and urine output. One critically ill child died during resuscitation. Sixteen patients were subjected to immediate surgery of whom 13 (81 per cent) required intestinal resection. In the remainder, after detorsion of the volvulus, the worm mass was extracted via an enterotomy.

Twelve patients, without initially compelling features, were managed with intravenous fluids, nasogastric decompression, antispasmodics and periodic clinical review for periods of 4 h to 5 days (mean 1·4 days). All were finally subjected to surgery because of clinical deterioration or failure to progress. Nine (75 per cent) required intestinal resection.

Intraluminal piperazine was instilled via the site of enterotomy or resection using a Foley catheter upon which the bowel was 'telescoped'. The bowel was closed in two layers with absorbable suture material, and peritoneal lavage with copious warm saline was performed before abdominal closure.

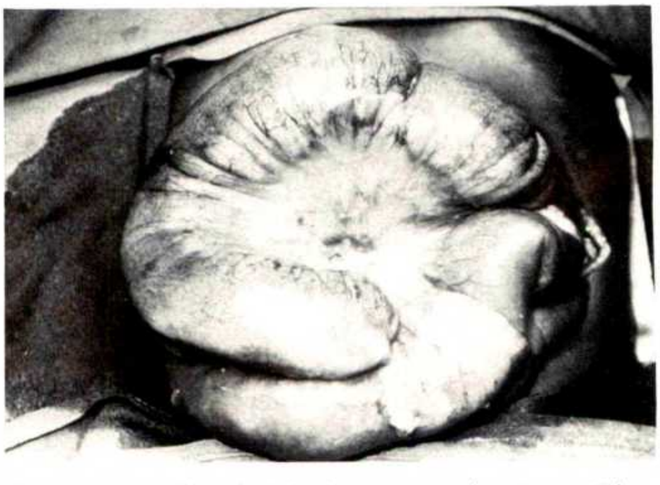

Figure 1 *Mid small bowel volvulus demonstrating ischaemic necrosis due to ascariasis*

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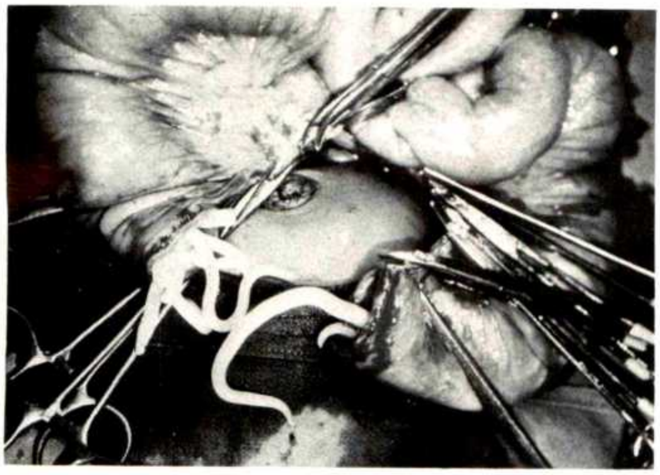

Figure 2 *Operative appearances after resection of ischaemic bowel showing adult ascaris worms at margins of resection*

Results

Mortality

Five children (17 per cent) died. All had presented as acutely ill patients requiring urgent surgery and all had gangrenous bowel. One child died during resuscitation; three children died after hypotensive episodes during surgery, of which two reflected inadequate pre-operative fluid replacement or endotoxaemia and one the inappropriate use of spinal anaesthesia. These deaths occurred 1 h to 3 weeks postoperatively. One child died of the sequelae of anastomotic disruption, peritonitis and septicaemia 3 months after surgery.

Morbidity

Twenty-one patients (72 per cent) required intestinal resection, eight of whom required resection of the terminal ileum. After intestinal resection two patients suffered anastomotic dehiscence, one of whom ultimately died, the other required parenteral nutrition and further surgery before recovery. Neither of these anastomotic failures could be attributed to residual enteric worms. No specific morbidity related to detorsion of a viable volvulus, or to formal enterostomy.

Discussion

In endemic areas the diagnosis of ascariasis is not difficult but the recognition of those few children who require surgery for existing or developing complications, among the large numbers who respond to conservative treatment, may not be easy. The emission of adult worms in vomitus or stool does not directly inculpate the worm as the cause of acute pathology. It may, unfortunately, be seen by parent or primary attendant as an indication to 'de-worm' a child using freely available vermifuges based on piperazine citrate which act by paralysing the parasite and rely upon bowel motility to evacuate the offender.

Although no direct evidence exists to associate vermifuge with volvulus, it would seem irrational to paralyse a bolus of worms which is causing intraluminal obstruction, complete or incomplete, thereby ensuring that spontaneous disentanglement cannot occur. The consistent operative finding of a mass of worms within the closed loop suggests that such a bolus may act as a relatively fixed point, allowing volvulus to occur[7] (*Figure 2*).

In 38 per cent of our patients a history of vermifuge was elicited, although this is likely to be an underestimate. Patients from whom such a history is obtained should be carefully evaluated, and the administration of vermifuge should normally be avoided in the symptomatic child and delayed until all symptoms have abated.

The distinction between volvulus and simple obstruction in these circumstances can be difficult, and the relative rarity of the former militates against early recognition. Nearly half of our patients presented clinically and radiologically as cases of simple bolus obstruction and, indeed, may have developed closed loop obstruction while undergoing conservative treatment. Although plain radiology failed to show typical features in 69 per cent of patients who were found to have enteric volvulus, radiology remains an essential investigation[7]. It is currently our policy to re-evaluate radiologically all patients with bolus obstruction in whom no clear evidence of clinical progress has been recorded at 12 h in an attempt to recognize the pre-ischaemic volvulus. All patients with simple obstruction are monitored in hospital until normal bowel function has returned after appropriate vermifuge.

When volvulus is suspected, resuscitation before surgery is mandatory. Forty per cent of deaths in our patients were directly attributable to intra-operative perfusion inadequacies, secondary to inadequate pre-operative resuscitation. Where intestinal resection is unnecessary, we prefer to remove worms via an enterotomy rather than 'milking' worms distally to the colon. The latter manoeuvre is difficult and traumatic to the bowel wall and provides no guarantee against small bowel re-infestation. We instil piperazine along the length of the bowel intra-operatively to minimize the risk of worm disruption of suture lines. Broad-spectrum antibiotic cover against aerobes and anaerobes is administered and primary closure of the superficial layers of laparotomy wounds is avoided in patients in whom intestinal resection was necessary.

Volvulus is a rare but devastating sequel to ascaris infestation, and may complicate the course of simple bowel obstruction, particularly after inappropriate vermifuge. Clinical vigilance is essential to minimize the high mortality and morbidity. Terminal ileal resection, in rural third-world communities where patient follow-up may be difficult, is potentially a source of major late morbidity, justifying an aggressive attitude to early diagnosis.

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Pancreatic abscess: results of prolonged irrigation of the pancreatic bed after surgery

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The mortality from pancreatic abscess may approach 70 per cent and the survivors often require repeated operations to debride the pancreas and to drain recurrent abscesses. We report the results of prolonged irrigation of the pancreatic bed after surgical débridement in 11 patients. Surgery was performed at an average of 17 days (range 8–25 days) after the onset of symptoms. The pancreatic slough was thoroughly debrided and 2–6 large drains were placed in the pancreatic bed. Irrigation with saline or Diaflex® solution (2–6 l/day) was started after 2 days and continued for a mean of 25 days (range 5–54 days). There were three deaths (27·3 per cent) after surgery: one of these patients required re-operation and packing for massive postoperative haemorrhage and all three had some evidence of persisting sepsis at autopsy. Prolonged irrigation of the pancreatic bed after surgical débridement may reduce mortality and the need for repeated drainage procedures in patients with pancreatic abscess, but the detection and treatment of persisting sepsis remains the major problem.

Keywords: Pancreatic abscess, pancreatitis, drainage

Acute pancreatic abscess formation is an uncommon complication of acute pancreatitis occurring in 1–9 per cent of patients[1–3]. Nevertheless, it is associated with a reported mortality of 14–67 per cent[4–11] and remains extremely difficult to treat. The most important aspect of management is wide surgical exploration and drainage. However, this may be associated with a 30 per cent incidence of recurrent abscess formation[12,13] and Ranson has suggested that management should include systematic drainage of all the abscess extensions using continuous irrigation and suction to sump drains[13]. Other groups have described a similar technique which they call complementary retroperitoneal lavage[14,15].

In this report we present our experience with prolonged irrigation drainage of the pancreatic bed after débridement for pancreatic abscess. We have included only those patients with infected peripancreatic fluid collections in association with significant tissue necrosis: hence, cases of simple pseudocyst and infected pseudocyst or pseudocyst abscess have been specifically excluded. These latter complications have a distinctly different anatomy; by definition they are strictly localized and have an encapsulation sufficiently firm to contain fluid contents and to hold sutures. Similarly, a discrete necrosis of the gland contained within its capsule has been excluded.

Patients and methods

During the 12-year period 1974–85, 156 patients with acute pancreatitis have been managed in a consecutive personal series and 11 of these (7 per cent) developed acute pancreatic abscess. There were six men and five women with an average age of 54 years (range 28–83 years). The severity of the initial attack of acute pancreatitis was assesses according to Ranson's grading system[2] and all 11 cases were defined as severe, with an average of 4·7 positive prognostic signs. In eight cases the initial acute pancreatitis was associated with gallstones and in five of these a pancreatic abscess developed as a postoperative complication of surgery for gallstones. In two, the pancreatitis was idiopathic and one was alcohol related. The presenting clinical features were tachycardia and fever (11), pain (10), a mass (8) and jaundice (5). The average period from admission to definitive surgery was 17 days (range 8–25 days). The patients were all gravely ill with a falling haemoglobin level (mean decrease = 24·4 per cent of admission level), a leucocytosis (mean $20{\cdot}9 \times 10^3/\text{mm}^3$) and hypo-albuminaemia (mean 27·1 g/dl). However, the amylase level was usually normal by the time that the diagnosis of pancreatic abscess was made (*Table 1*).

The operation of débridement was carried out through a long midline incision. Gentle digital dissectionremoved the pancreatic and peripancreatic slough and opened the cavities and their extensions into the paracolic gutters, behind the mesocolon and around the kidneys and spleen. A minimum of two and up to six tube drains were placed into the cavities through lateral stab incisions; 28–32 Ch diameter Argyle chest drains or Robinson drains (H. G. Wallace Ltd, Essex, UK) and 45 cm long were used. From the first postoperative day the tubes were irrigated with 2–6 litres of saline or Diaflex (Boots plc, UK) no. 61 solution. The irrigation solution was connected to a Higginson's bulb, which is a two-way drainage system better known as part of the urologist's armamentarium for postoperative bladder irrigation. After filling the system with irrigation fluid, manipulation of the bulb at the inflow channel allows vigorous flushing followed by drainage to a collecting bag. The swirling action so created is particularly successful in dislodging particulate matter and surprisingly large quantities of necrotic slough are removed by this method. Irrigation was discontinued when the usual signs of continuing sepsis had resolved and the irrigant fluid was returned clear. Sinograms were also used in five patients to assess the rate of resolution.

Postoperatively all patients were managed with nasogastric aspiration, intravenous feeding and broad-spectrum antibiotics. Ten out of eleven patients required mechanical ventilation for a mean of 11 days (range 2–31 days) and one patient received haemodialysis for renal failure.

Results

A summary of the results is presented in *Table 1*. Three patients died after débridement at 5, 12 and 26 days. In the first two, post-mortem examination demonstrated an abscess above and behind one kidney, which had been missed at the débridement operation. The third patient required reoperation 24 h after débridement for packing of a bleeding cavity. He subsequently developed jaundice and renal failure and died 25 days later. At autopsy there was evidence of continuing retroperitoneal necrosis and sepsis.

Four patients came to laparotomy within 48 h of admission because of failure to respond to full conservative therapy and to exclude other pathology. All were found to have acute pancreatitis associated with gallstones and this was complicated

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Table 1 *Clinical data on 11 patients with pancreatic abscess*

Patient	Age	Sex	Presenting features	Haemoglobin (g/dl)*		WCC ($10^3/mm^3$)	Albumin (g/dl)	Amylase (IU)	Extent of abscess	Duration of irrigation (days)	Complications
				Admission	Pre-op						
1	67	M	Fever, jaundice, mass LIF	15·8	12·3 (22·2)	26·5	26	160	Head pancreas, bile duct, R paracolic gutter.	29	Biliary fistula, closed spontaneously
2	35	M	Fever, epigastric mass, jaundice	13·4	10·2 (23·9)	11·8	25	158	Body pancreas lesser sac, mesocolon	10	Upper GI bleed managed with pitressin
3	73	F	Fever, mass	12·6	10·7 (15·1)	15·9	23	—	Head pancreas bile duct, R paracolic gutter	47	Biliary fistula, closed spontaneously
4	36	M	Fever, pain	14·8	11·5 (22·3)	15·3	32	200	Body pancreas lesser sac	54	Wound infection and dehiscence.
5	46	F	Fever, pain mass L loin	14·7	10·2 (30·6)	19·3	19	95	Head and body panc spleen, L paracolic gutter.	35	Pleural effusion diabetes
6	61	F	Fever, epigastric mass	12·5	8·5 (32·0)	15·6	34	285	Head and body panc	5	Chest infection Died, PM, abscess R kidney
7	28	F	Fever, pain	12·0	9·5 (20·8)	12·0	36	100	Tail pancreas, spleen, L paracolic gutter	23	Pulmonary embolism Gastric fistula closed spontaneously
8	83	F	Fever, epigastric mass	12·5	9·4 (24·8)	21·0	24	106	Body pancreas, lesser sac, porta hepatis, mesocolon.	16	Pleural effusion
9	45	M	Fever, pain, epigastric mass, jaundice	18·6	12·2 (34·4)	37·0	29	158	Body and tail pancreas, lesser sac	26	Haemorrhage from pancreatic bed jaundice, renal failure Died, PM, retroperitoneal sepsis
10	56	M	Fever, pain, jaundice	15·6	11·5 (26·3)	21·3	28	110	Body pancreas, L paracolic gutter lesser sac, porta hepatis	12	Chest infection, jaundice. Died, PM, abscess L kidney.
11	63	M	Fever, mass, pain, jaundice	12·2	10·2 (16·4)	33·8	22	233	Body pancreas, lesser sac, spleen, L paracolic gutter, small bowel mesentery.	18	Upper GI bleed

*Percentage fall in haemoglobin is shown in parenthesis LIF, left iliac fossa

by biliary peritonitis in one patient. In each case a cholecystectomy was performed and in three the common bile duct was explored and stones were removed. Despite drains being placed around the pancreas, all these patients required a second operation for pancreatic abscess. A fifth patient also developed a pancreatic abscess following cholecystectomy. This operation was performed routinely at a previous admission and the common bile duct was not explored. Subsequently the patient was re-admitted with a pancreatic abscess and a definitive drainage was carried out 90 days after the original cholecystectomy. At the definitive débridement procedures, a further three patients were found to have gallstones and underwent cholecystectomy: however, stones were found in the common bile duct in only one case (*Table 2*).

At the débridement operation, sepsis and necrosis were confined to the immediate area of the pancreas in three patients. In the remaining cases the abscess had also spread to the mesocolon (two cases), down one of the paracolic gutters (six), around the spleen (three) and into the porta hepatis surrounding the bile ducts (four). Histologically proven infarcted pancreas was found in two cases.

The average duration of hospital stay was 67 days (range 25–143 days). Irrigation through the drainage tubes was continued for a mean of 24 days (range 5–54 days) and lumps of necrotic material and pus were seen to be washed out for a considerable time after surgery. The major complications are summarized in *Table 1*. All three fistulae (two biliary and one gastric) closed spontaneously. The bacteriological data are presented in *Table 3*; it was of interest that positive cultures were obtained in only two out of eleven cases.

Discussion

Diagnosing pancreatic abscess may be difficult[8,9,16] but, in the group of patients presented here, a persisting tachycardia and fever 10 days after admission, together with a leucocytosis, hypo-albuminaemia and a falling haemoglobin were all useful signs. Thus the diagnosis was clinical and established by simple features. Although we have no experience with it, CT scanning has recently been reported both as an accurate diagnostic tool[6,17] and as a good method of assessing the extent of a pancreatic abscess[18]. Furthermore, after the administration of an intravenous contrast medium, the degree of enhancement of the pancreas has been used to predict which patients with acute pancreatitis will go on to develop pancreatic abscess[19]. It has also been suggested that ERCP may be useful in the assessment of patients with pancreatic abscess by demonstrating disruption of the pancreatic duct system[20,21].

Much of the difficulty in the management of pancreatic abscess derives from confusion in nomenclature[22]. The pathological process involved in the cases described in this report is extensive and progressive pancreatic and peripancreatic necrosis, leading to the accumulation of slough and/or pus in the retroperitoneum. This pathology is known to have a significant mortality and should not be confused with secondary infection of a pseudocyst, where the mortality is low.

Table 2 *Biliary surgery in eight patients with pancreatic abscess*

Patient	Time before débridement (days)	Cholecystectomy	Gallbladder stones	On table cholangiogram	Exploration of CBD	Duct stones	T-tube
Before débridement ($n=5$)							
3	16*	+	+	–	+	+	+
9	18	+	+	–	+	+	+
6	20	+	+	–	+	+	+
7	90†	+	+	+	–	–	–
11	23	+	+	–	+	+	+
At débridement ($n=3$)							
1	—	+	+	+	+	–	+
8	—	+	+	+	–	–	–
5	—	+	+	+	+	+	+

* Presented with biliary peritonitis and pancreatitis (site of biliary leak not established); † a previous admission with pancreatitis, the subsequent ERCP was normal

Table 3 *Bacteriology in 11 patients with pancreatic abscess*

Patient	Abdomen/pancreas	Drain	Blood culture
8	*E. coli* Yeasts	—	—
2	Micro-aerophilic streptococci *E. coli* *Streptococcus faecalis*	*E. coli*	—
5	—	*Staphylococcus albus* *S. faecalis*	—
7	*E. coli*	—	—
1	*E coli*	*S. faecalis* *E. coli* *Pseudomonas*	—
9	*E. coli*	*E. coli*	*E coli*
4	*E. coli*	—	—
3	*E. coli*	—	—
6	*E coli*	—	*E. coli*
10	*E. coli*	—	—
11	*E. coli* *S. faecalis* *Proteus*	*E coli* *S. faecalis*	—

Although it is generally accepted that adequate surgical drainage is the cornerstone of successful treatment in pancreatic abscess, there has been no consensus as to the optimum method of achieving this end. Attempts to compare the results of alternative methods of treatment are hampered because, first, there are no controlled trials of effectiveness and, second, there has been considerable inconsistency in the definition of pancreatic abscess used in different studies.

An anterior transperitoneal approach to the abscess has been favoured by most[14,15] but a posterior flank approach has also been utilized with success[23] and may be of particular value in localized abscesses of the tail of the pancreas[24]. Others have advocated synchronous anterior exploration and posterior dependent drainage through the bed of the resected twelfth rib[25] but this has not enjoyed widespread use.

Irrespective of the approach used, the major problem has been continuing necrosis and sepsis requiring repeated drainage in up to 30 per cent[13]. This is the major cause of mortality and remains the main challenge in developing successful treatment for pancreatic abscess. An open packing technique[6] and marsupialization[7] are suggested methods of reducing the need for repeated drainage procedures. Bradley and Fullenwider[6] reported a 14 per cent mortality rate in patients treated by open packing but not all results are so impressive. For example, Mughal *et al.* have recently demonstrated that this technique is successful in preventing residual intra-abdominal abscess, but concluded that there was no dramatic effect on survival with a mortality of 46 per cent in their 13 cases[26].

Closed drainage with continuing local lavage via catheters placed in the cavities left after débridement has also been advocated as a method of improving results[13,27]. However, several groups have commented on the difficulty in draining particulate matter by way of Penrose or sump drains[8,9]. We have therefore modified the technique by the addition of a two-way urological drainage system to the lavage apparatus and we have been impressed by the volume of particulate matter washed out of the abscess cavities by this method.

Good results can be achieved only if careful attention is paid to the details of the débridement operation. Exploration, débridement and drainage must be extensive, otherwise the extent of an abscess may be underestimated[4]. Two of the patients who died in our series had an abscess extension in relation to one kidney missed at the débridement operation. Thus, we regarded their deaths as the result of an inadequate initial drainage procedure rather than a failure of the subsequent drainage system. None the less, the process of retroperitoneal liquefaction is progressive and prolonged irrigation drainage of the pancreatic bed is required. Persisting retroperitoneal sepsis remains the main problem in the treatment of pancreatic abscess by this method; however, serial CT scanning should demonstrate those patients with residual abscesses and hence the need for further surgery. In such instances the open packing method of Bradley[6] may prove to be a more appropriate secondary procedure.

The timing of surgery is critical, and our policy has been to wait as long as possible and always beyond the eighth day, so that the boundary between viable and non-viable tissue will be clear. The dendritic extensions of the infective process are clearly defined and, although the operation may of necessity be extensive to guarantee total exploration of all the cavities, a thorough complete procedure is more likely.

Although this small series is uncontrolled, our results support the use of wide exploration and drainage followed by prolonged irrigation of the pancreatic bed. The presence of particulate amorphous material in the lavage effluent for several days after débridement suggests that the technique of irrigation is effective. Furthermore, there were no complications resulting from the use of wide-bore drainage tubes. Prolonged irrigation of the pancreatic bed after débridement may reduce the mortality from pancreatic abscess and the necessity for repeated drainage procedures, and is worthy of further evaluation.

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Paper accepted 14 July 1987

Correspondence

Ultrasound-guided percutaneous drainage of intra-abdominal abscesses

Sir

I read with interest the paper by Lameris *et al.* (*Br J Surg* 1987; **74**. 620–3) which promotes the extended use of ultrasound-guided percutaneous drainage of intra-abdominal abscesses.

The authors demonstrate again that infected, non-viscous, intraperitoneal collections can be localized by ultrasonography and drained by needles or tubes, and that the latter can be advanced with relative safety through various abdominal organs and cavities. In addition, we are told that 'with this strategy a high percentage (89 per cent) of patients with intra-abdominal abscesses can now be cured'; that the percutaneous method is a less invasive treatment than surgical drainage and, therefore, it is 'the only possible approach' in critically ill patients and that 'in the event of insufficient drainage, placement of a second or larger catheter should be considered'.

Although we have no doubt that some intraperitoneal septic collections respond to percutaneous drainage, we must disagree with some of the authors' conclusions and recommendations.

The reported mortality rate of 11 per cent applies to the group of patients with intra-abdominal abscesses referred to the authors for percutaneous drainage; it does not mean that this treatment modality cures 89 per cent of the patients with intra-abdominal abscesses. No mention is made of the number of patients who succumbed to intra-abdominal infection during the study period but were not offered percutaneous drainage. Another mystery not brought to our attention is the severity of illness and the physiological reserve of the reported patients, which naturally would have a major influence on the final outcome.

There is abundant evidence in the literature to suggest that delay in the control of intra-abdominal infection is an important factor contributing to high mortality rates. Using the words of Lameris *et al*, we postulate that 'eight (patients) died from sepsis due to inadequate drainage' probably because 'critically ill patients for whom percutaneous drainage was the only possible approach' were denied prompt and complete surgical eradication of intra-abdominal infection.

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Author's reply

Sir

I would like to comment on some of the remarks made by Dr M Schein.

As an observant reader he should have noticed that the 89 per cent cured patients with intra-abdominal infection was achieved with the combination of percutaneous abscess drainage (PAD) and surgical drainage.

Certainly the mortality rate of 11 per cent does not apply to a group of patients 'referred to the authors' for percutaneous drainage. Most of the patients were treated in the surgical department (J. Jeekel) and either operated and/or drained percutaneously.

In the event of insufficient drainage not only placement of a second or a larger catheter should be considered, but also surgical drainage Of the eight patients who died with sepsis after unsuccessful PAD, five patients died after subsequent laparotomy and one patient after direct surgical drainage.

I would like to stress the fact that there are certain patients in whom percutaneous drainage is applied as a last effort. As for many interventional radiological procedures, these patients were often the first in whom these new techniques have been applied

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Ascaris lumbricoides and intestinal perforation

Sir

We write with reference to Efem's review (*Br J Surg* 1987; **74**· 643–4) which states that despite a careful 4·5 year search no evidence to support ascariasis as a cause of intestinal perforation was found. The following is one such case.

A 58-year-old Bangladeshi man was admitted with a 20-hour history of progressive central colicky abdominal pain and nausea On examination he was distressed, pyrexial (38·8°C), and his pulse was 85 beats/min. His abdomen was distended with guarding and rebound tenderness in the right iliac fossa. Appendicitis was diagnosed.

At laparotomy a segment of ileum 13 cm long, 50 cm from the ileocaecal junction was found to be diffusely inflamed and perforated. The adjacent mesentery was involved in suppuration. Two long cylindrical structures were palpated within the lumen of the small bowel A limited small bowel resection was carried out. An *Ascaris lumbricoides* worm was extracted from the excised segment; the latter was carefully examined and found to be perforated; histological examination confirmed the perforation, the serosal surface of the bowel showing fibrinous exudate and suppuration.

The patient has been a permanent local resident since 1981 when he was found to have an unexplained 10 per cent eosinophilia. A detailed history and histological examination of the resected bowel did not reveal amoebiasis or typhoid, which would predispose toward intestinal perforation, or ulcerogenic drugs such as Slow K (Ciba Laboratories, Horsham, UK). In conclusion, this was a case of ileal perforation directly attributable to *Ascaris lumbricoides*

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Anastomotic recurrence in large bowel cancer

Sir

I was interested to read the recent review by Henry Umpleby and Professor Williamson (*Br J Surg* 1987; **74**. 873–8) where they clearly focus attention on the ways that anastomoses may influence subsequent tumour formation either through the process of implantation of viable malignant cells or through the development of a second primary tumour there They describe some steps that surgeons may take to minimize implantation such as the use of intraluminal cytotoxic agents but fail to mention the role of suture material in this regard. O'Dwyer and his colleagues have shown that there is considerable variation in the way that cancer cells adhere to different suture materials *in vitro* and found Prolene to be the 'best' followed by chromic catgut, nylon, silk and vicryl in descending order[1]

As far as the induction of new primary tumours is concerned, there is evidence that the choice of suture material plays a role here also[2,3]. In an experimental rodent model the colon carcinogen dimethylhydrazine given 2 months after construction of a colonic anastomosis, either with stainless steel wire or with silk, induced significantly more primary tumours when wire had been used[3] Although this raises broader issues in regard to the safety of staples, and although it is clear that a mechanism does exist for suture materials to influence both recurrence through second primary tumour formation and through facilitating the transfer of exfoliated cancer cells, one must of course be wary of extrapolating too much from an animal model to man.

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Record number of gallstones

Sir

Martin and Jackson's finding of 23 530 gallstones in a single gallbladder is indeed remarkable (*Br J Surg* 1987; 74: 704). In recent years, the record number of gallstones reported in the literature has become a favourite question asked of the students on surgical rounds. A review of the literature uncovered a case report, from this institution, by Schenken and Coleman who in 1945 noted 36 329 gallstones in an otherwise normal gallbladder. This may be the record

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1. Schenken JR, Coleman FC. Cholelithiasis: report of a case with 36 329 stones in the gallbladder. *Gastroenterology* 1945; 4: 344–6.

Assessment of hospital workload in war surgery

Sir

I whole-heartedly agree with the recent report by Ph. Gertsch (*Br J Surg* 1987, 74: 831–3) detailing the handling of casualties during the summer of 1985 when a major battle took place near the Pakistan border

As exemplified by the Falklands campaign, the principle aim of war surgery is to offer a chance of survival to the greatest number of wounded[1]. To this end the Triage System used by the British Forces ensures that those casualties in urgent need of surgery are selected first even though their operations may well be lengthy. Thus, patients with severe injuries are given a real chance of survival Such a selection procedure avoids the pitfall of treating 'minor' cases, who could survive without early surgery, just because the operative time for such surgery would be short.

Let us hope that all warring nations take heed of our experience and alter their own handling of casualties.

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Bacterial growth kinesis in generalized peritonitis

Sir

May we correct a factual error in the letter by Krukowski and Matheson in your correspondence column of October 1987.

Neither Noxyflex nor Taurolin rely on formaldehyde release for their activity. Recent studies have shown that the level of free formaldehyde in noxythiolin is extremely low[1] and that these levels are too low to account for the antimicrobial activity observed[2].

Taurolin contains only trace amounts of free formaldehyde (less than 0.0038 per cent[3]) and this fractional component makes no contribution whatsoever to its antimicrobial activity[4]

The anti-adherence effect of Noxyflex has been shown to be produced by the noxythiolin molecule itself and none of its breakdown products have a similar effect[5].

Taurolin is known to rely on the transfer of methylol groups to the bacterial cell wall for its bactericidal activity These same methylol groups cross-link endotoxins and deactivate them, thus explaining the pronounced anti-endotoxin activity. The anti-endotoxin activity of Noxyflex is thought to be by the same mechanism[6].

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Book reviews

Andrology

J. P. Pryor and L. L. Lipshultz. 168 × 240 mm. Pp. 340. Illustrated 1987. Guildford: Butterworths. £50.00.

For many years male sexual disorders and male infertility have received scant attention from most practising urologists. However, in the past 5 years there has been a considerable interest in all aspects of andrology which is rapidly becoming a sub-specialty within urology.

John Pryor and Larry Lipshultz have combined to produce a superb overview of andrology with contributors from both sides of the Atlantic (and one from Australia) many of whom enjoy an international reputation. The text is comprehensive and covers all aspects from intersex through congenital disorders, erectile and ejaculatory dysfunction and male infertility.

Recent developments in andrology are well covered (for example the latest types of inflatable penile prosthesis) but I was surprised to find no mention of percutaneous transcatheter embolization of varicoceles in the chapter on 'The surgical management of male infertility'. The otherwise excellent chapter on penile torsion, curvature and Peyronie's disease is rather dismissive of other methods of surgical treatment of penile deformity and the reader is left with the impression that there is only one operation which should be performed for correction of Peyronie's disease.

The text is comprehensively referenced although cross reference between chapters is non-existent. Typographical errors are few, the text is clearly laid out and well illustrated. The detailed chapters on intersex, pathophysiology of priapism, physiology of ejaculatory disturbances and hormone function and regulation of the prostate should make this book essential reading for the urological trainee (and for those of their trainers who seek the same knowledge), whilst chapters on congenital and acquired erectile disorders provide useful guidelines for those surgeons seeking advice about the management of an occasional or unusual case. I hope that this book will be purchased for urological libraries. However, its price makes it unlikely that it will be purchased by individuals other than those with a great interest in the subject.

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Cancer Surveys. Volume 5 Number 3. Hormones and cancer: 90 years after Beatson

R. D. Bulbrook. 155 × 234 mm. Pp. 692. Illustrated. 1986. Oxford: Oxford University Press. £13.50.

The link between the chapters in this book is that breast cancer, prostatic cancer and endometrial cancer are hormone dependent tumours. This book is therefore of potential interest to endocrine biochemists but not of great interest to surgeons since the individual surgeon will tend to concentrate on either breast or prostatic cancer.

The list of authors is impressive and contains most of those who are known in this field. Each chapter is written by an enthusiast and the book is, therefore, very much loaded in favour of the importance of hormones and endocrine receptors in the breast cancer field, resulting in over-stressing their usefulness. For example, the chapter by Maguire on 'Prognostic factors in breast cancer' starts with the assumption that the oestrogen receptor is the most powerful prognostic factor that we have. This would not be in accordance with the findings of many other groups working in the prognostic field.

In summary, it is not a book for the surgeon unless he is super-specializing in the field of breast cancer, in which case it will be a useful reference edition although he probably knows most of the work contained.

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Davey's Companion to Surgery in Africa. Second Edition

A. Adeloye. 195 × 255 mm. Pp. 486 + xii. Illustrated. 1987. Edinburgh: Churchill Livingstone. £40.00.

The second edition of *Davey's Companion to Surgery in Africa* is welcome. For nearly 20 years this Companion has been used by doctors and medical students alike throughout Africa. The second edition has been enlarged and updated. The Editor has made good use of advisors and contributors to produce an accurate description of the common diseases peculiar to tropical Africa. The first 15 chapters, nearly half of the book, deal adequately with conditions which present themselves in out-patient clinics in Africa. The expanded text on these subjects will be particularly useful to doctors and students faced with diagnostic perplexities. The chapters on ulceration and gangrene and pyomyositis are very fully described. The subject matter is presented clearly with helpful diagrams and good photographic illustrations. The references are abundant and well selected but are virtually all before 1980. This may reflect the delay in completion which is explained in the preface.

The second half of the Companion deals with more general surgery. This is written to highlight conditions which present themselves most commonly in Africa. All subjects are treated well and, in particular, surgical conditions of the spleen, volvulus and the management of strangulated and other complicated hernias. The statistical variation in such diseases as peptic ulceration and intra-abdominal malignancy is noted. In this section also, there is good illustration with diagrams and photographs.

Medical students and doctors intending to practice in non-specialist centres in the tropics would be well advised to acquire a copy of this edition of *Davey's Companion to Surgery in Africa.*

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Surgical Lasers

T. A. Fuller. 190 × 265 mm. Pp. 237. Illustrated. 1987. Basingstoke: Macmillan. £68.00.

Current clinical applications of lasers are reviewed in an extremely well-written and illustrated text which gives a thorough and balanced view of what lasers can and cannot do in the current state of the art. The introductory chapter on laser fundamentals is easy to understand although it would have been nice to have included more information on the nature of the interactions between laser light and living tissue before going into specific clinical applications. Chapters on well-established applications, as in gynaecology and ENT surgery, give clear indications and practical guidelines on technique. Chapters on endoscopic use in the gastrointestinal, respiratory and renal tracts also give excellent surveys of when laser therapy is likely to be of value. The section on dermatology gives a refreshingly honest analysis of treatment results with photographs of lesions before and after therapy that give a true comparison. The editor is to be congratulated on resisting the temptation to include chapters on the two hottest topics of current laser research, namely angioplasty and photodynamic therapy—both have enormous potential, but neither is yet established in clinical practice. This is an excellent book and recommended to all those with an interest in the current use of lasers.

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Mastery of Surgery

L. M. Nyhus and R. J. Baker. 285 × 220 mm. Pp. 1540 + xxxviii + 26. Illustrated. 1987. Edinburgh: Churchill Livingstone. £45.00

The corpus of general surgical operations is now so extensive that no single teacher, and few groups of hospital consultants, can give expert practical instruction across this full spectrum. *Mastery of Surgery* attempts to overcome this problem. Its two editors, both acknowledged teachers and experienced authors, have selected an international group of contributors—from Europe, the UK, Australasia and South Africa as well as from the USA.

There are introductory chapters on the preparation of the patient, metabolic response to trauma, anaesthesia, fluid balance, postoperative care and surgical bacteriology. The main bulk of the work concentrates on major surgery of the head and neck, breast, oesophagus, the abdominal cavity (including gynaecological surgery), hernia, the urinary tract, peripheral vascular surgery and the surgery of the hand. Surgical anatomists provide excellent introductions to each major topographical region. Specific operations together with indications and results, are fully described and beautifully illustrated by copious line drawings. In many cases, two separate authors describe the same procedure—something that has been criticized by other reviews. Personally, I found it refreshing to see controversial matters debated in this way; after all, this is what happens in practice! Moreover, the two editors provided pithy comments at the end of each chapter, not always entirely complimentary, that supplement the debate. This is an interesting and stimulating contribution to the texts on general operative surgery. It is one that certainly educates the surgical trainee as well as one that will enterain his trainer.

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Complications of Paediatric Surgery

J. Lister. 175 × 250 mm. Pp. 282. Illustrated. 1986. Eastbourne: Baillière Tindall. £29.50

The series editor intends this book to be 'directed at all surgical trainees and at consultants outside referral centres'. Certainly a general surgeon with paediatric practice will find it of interest in the relevant chapters, particularly those on the alimentary tract which takes up a third of the book, and the genito-urinary tracts. The trainee in paediatric surgery has two main concerns, to prepare for consultant practice and to pass a specialist fellowship examination. This book is not sufficient for these purposes. The recommended reading list contains remarkably few references after 1981 and sections on neonatal surgery and intensive care are too brief. Many complications arise in the management of the premature new born and as a result of intravenous nutrition, but these topics get little attention.

This book can therefore be recommended for general surgeons with a major interest in paediatric surgery, but the restrictions inherent in the series editor's Forward make it impossible to recommend this book to anyone working in a referral centre.

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Principles and Practice of Surgical Stapling

M. M. Ravitch and F. M Steichen. 235 × 155 mm. Pp. 539 + xix. Illustrated. 1987. Chicago. Year Book Medical Publishers.

From the title of this book one would expect to find a comprehensive textbook on surgical stapling. Unfortunately this is not the case. The book is in fact the proceedings of a symposium on surgical stapling held in Pittsburg in 1986 and, as with many proceedings, there is considerable repetition. There are also several important omissions. For instance, the topics of gastric stapling techniques for morbid obesity, or the use of staples in gynaecology and urology are not covered. There is no attempt to quantify cost effectiveness of stapling.

The book itself is divided into five sections. The first section is on stapling in general and includes chapters on the mechanics of stapling and experimental studies of staple healing. There are then sections on benign oesophageal disease, carcinoma of the oesophagus, pulmonary resections and colorectal surgery In these four sections there is considerable repetition, there being no less than eight chapters on anterior resection The book is extensively illustrated and the illustrations on the whole are of high quality. This is not a book for the surgeon who is unfamiliar with the use of staples The book assumes a working knowledge of the instruments and the basic techniques. For the surgeon already conversant with stapling there are many useful hints to be gleaned and there are extensive references at the end of each chapter.

I think this book would be a very useful addition to a medical library but I doubt if many surgeons would wish to purchase it for themselves.

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Self Assessment Exercises in Surgery

W. E. G. Thomas. 210 × 198 mm Pp. 164. Illustrated. 1986. London Butterworths. £19.50.

The final FRCS examination is regarded as a difficult exam to pass. The standards set by examiners are high and the level of clinical 'experience' which would make passing the examination easier is never really achieved until some time after the hurdle has been overcome. Most textbooks designed to help candidates prepare for such an exam will be strong on theoretical surgery but cannot compensate for the lack of exposure to clinical cases or examination method. This book is designed to help with this problem by simulating the clinical and viva parts of the final FRCS. It contains six question and answer sections dealing with clinical cases, clinical radiology, operations, pathological specimens, instruments and microscopical pathology The initial questions are designed to test the reader's power of observation, and skilful subsidiary questioning assesses the reader's clinical decision-making and general surgical knowledge. The clinical colour photographs are excellent and the X-rays are clearly reproduced. The section on instruments will reassure candidates who feel vulnerable when instruments are being discussed—but be prepared for slightly less modern examples in the examination hall.

In summary, I think that this is an excellent book for FRCS candidates which will be of greatest use for revision between the paper and clinical parts of the FRCS examination

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Atlas of Gastrointestinal Endoscopy

F E. Silverstein and G. N. J. Tytgat. 310 × 250 mm. Pp. 350. Illustrated. 1987. Edinburgh. Churchill Livingstone £79.95

This large and well-produced atlas covers all aspects of gastrointestinal endoscopy including therapeutic procedures. The endoscopic photographs are of excellent quality and many are accompanied by labelled line drawings which usefully clarify the endoscopic appearances. The atlas would be a valuable reference source for any gastrointestinal surgeon or physician, and an instructive introduction for any endoscopist in training.

After an initial chapter on the normal appearances of the gastrointestinal tract, the book is divided into sections on diseases of the oesophagus, stomach, small bowel, and colon, together with one chapter on the endoscopic aspects of ERCP. There is an impressive collection of endoscopic photographs for each of these sections The majority of these photographs come from Dr Tytgat's unit in Amsterdam and will also apparently be available as a separate slide set Each chapter has a highly readable text which gives a brief description of the relevant anatomy, endoscopic technique, and the gastrointestinal diseases which may be encountered. Line diagrams, colour illustrations and X-rays are also included, generally with good effect. A comprehensive range of pathological conditions and the postoperative appearances are illustrated for each organ. Endoscopic interventional techniques are well described.

This book is highly recommended for any endoscopic unit as a reference source and teaching aid, and would be a popular addition to any medical library.

J. N. Thompson

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St. Mary's Hospital
London, UK

Notices and announcements

4–9 February 1988
54th Annual Meeting of the American Academy of Orthopaedic Surgeons
Atlanta, USA
Information Lois Stratmeier, 444 North Michigan Avenue, Suite 1500, Chicago, Illinois 60611-3981, USA

8–12 February 1988
Third Biennial Conference of the Indian Society of Oncology and the Indo–USSR International Workshop on Oesophageal Cancer
Bangalore, India
Information Conference Secretariat· Kidwai Memorial Institute of Oncology, Hosur Road, Bangalore-560 029-India

3–5 March 1988
1st International Congress on the Immune Consequences of Trauma Shock and Sepsis, Mechanisms and Therapeutic Approaches
Munich, FRG
Information Dr Eugen Faist, LM University Munich, Department of Surgery, Klinikum Grobhadern, Postfach 701260, D-8000 Munich 70, FRG

20–21 February 1988
First International Congress of the North American Society of Phlebology
San Diego, California, USA
Information: Helane Fronek MD, 3051 Cranbrook Court, La Jolla, California 92037. USA

4 March 1988
Angioplasty and Thrombolysis in Surgery
Nottingham, UK
Information. Mr B. R. Hopkinson FRCS, Consultant Surgeon, Queen's Medical Centre, University Hospital, Nottingham, UK

19–26 March 1988
6th Cardiosurgical Symposium
Zurs am Arlberg, Austria
Information. Prim Professor Dr M. Deutsch, Abtlg fur Herz-GefaBund Thoraxchirurgie, Krankenhaus de Barmherzigen, Schwestern vom Heiligen Kreuz, Grieskirchner Straße 42, A-4600 Wels, Austria

13–15 April 1988
Annual Meeting of the Association of Surgeons of Great Britain and Ireland
Harrogate, UK
Information· Mr B. T. Jackson, The Royal College of Surgeons of England, 35/43 Lincoln's Inn Fields, London WC2A 3PN, UK

28–30 April 1988
20th Congress of the European Association for Gastroenterology and Endoscopy (EAGE)
Sirmione, Italy
Information: Professor G. Bianchi-Porro (President EAGE), Ospedale 'L Sacco', Gastrointestinal Unit, 1-20157 Milan, Italy

17–28 April 1988
Advances in Neurosurgery
Glasgow/Edinburgh, Scotland, UK
Information: Director, Courses Department, The British Council, 65 Davies Street, London W1Y 2AA, UK

21–23 April 1988
2nd Symposium for Surgery on the Fetus
Gmunden, Germany
Information· Dr Wolfgang Metka, A-4020 Linz, Hauptplatz 29, Germany

28–30 April 1988
20th Congress of the European Association for Gastroenterology and Endoscopy (EAGE)
Sirmione, Italy
Information. Professor G Bianchi-Porro (President EAGE), Ospedale 'L Sacco', Gastrointestinal Unit, 1-20157 Milan, Italy

1–6 May 1988
Bicentennial Scientific Meeting Royal Australasian College of Surgeons
Brisbane, Australia
Information 1988 GSM, Royal Australasian College of Surgeons, Spring Street, Melbourne, Australia 3000

5–7 May 1988
Biennial Congress of the European Council of Coloproctology 1988
Geneva, Switzerland
Information General Secretary of the European Council of Coloproctology, Policlinique de Chirurgie, Hôpital Cantonal Universitaire de Genève, 1211 Geneva 4, Switzerland

8–11 May 1988
Joint Annual Meeting of the American Lung Association, the American Thoracic Society and the Congress of Lung Association Staff
Las Vegas, USA
Information Deborah Richardt, American Lung Association, 1740 Broadway, New York 10019, USA

12–14 May 1988
Second Vienna Shock Forum
Vienna, Austria
Information. AUSTROPA Kongbressbüro, Friedrichstrasse 7, A-1010 Vienna, Austria

23–28 May 1988
Advanced Hepato-Pancreato-Biliary Surgery
Lund, Sweden
Information· Professor Stig Bengmark, Box 5003, S-220 05, Lund 5, Sweden

25–28 May 1988
79th Annual Meeting of the American Association for Cancer Research
New Orleans, Louisiana, USA
Information. Margaret Foti, Executive Director, American Association for Cancer Research, Temple University School of Medicine, West Building Room 301, Philadelphia, PA 19140, USA

29 May–3 June 1988
Second World Congress on Hepato-Pancreato-Biliary Surgery
Amsterdam, The Netherlands
Information Q. A. Laman Trip, Organizer, Alton House, Keizersgracht 792, 1017 EC Amsterdam, The Netherlands

5–11 June 1988
Tropical Medicine Update
Liverpool, UK
Information· Director, Courses Department, The British Council, 65 Davies Street, London W1Y 2AA, UK

12–17 June 1988
Cardiovascular and Interventional Radiological Society of Europe
Berlin, FRG
Information: Dr Reingard Sörensen, Klinikum Steglitz, Röntgendiagnostik, Hindenburgdamm 30, 1000 Berlin 45, FRG

20–22 June 1988
7th International Workshop for the Study of Vascular Anomalies
Hamburg, Germany
Information. Dr John B. Mulliken, The Children's Hospital, 300 Longwood Avenue, Boston MA 02115, USA

3–9 July 1988
16th World Congress of the International College of Surgeons
Milan, Italy
Information Secretariat, Clinica Chirurgica III—Universitá degli Studi, Via F Sforza 35, 20122 Milan, Italy

6–8 July 1988
The Third British Arthroscopy Symposium
Harrogate, UK
Information Mr M. R. Phillips, Chas F Thackray Ltd., Shire Oak Street, Leeds LS6 2DP, UK

22–26 August 1988
Digestive Surgery in Video
Lund, Sweden
Information: Professor Stig Bengmark, Box 5003, S-220 05, Lund 5, Sweden

30 August–2 September 1988
10th World Congress Collegium Internationale Chirurgiae Digestive
Copenhagen, Denmark
Information. Secretariat, Spadille Congress Service, Sommervej 3, DK-3100 Hornbaek, Denmark

11–19 September 1988
XIIth International Congress of the Transplantation Society of Australia and New Zealand
Sydney, Australia
Information. Dr B. Hall, Honorary Secretary, Transplantation Society of Australia and New Zealand, 145 Macquaire St, Sydney 2000, Australia

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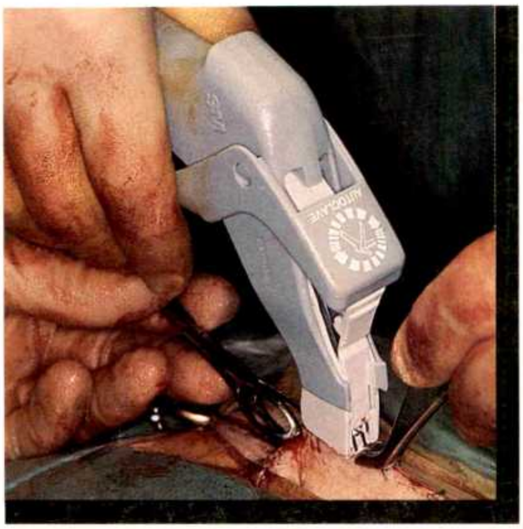

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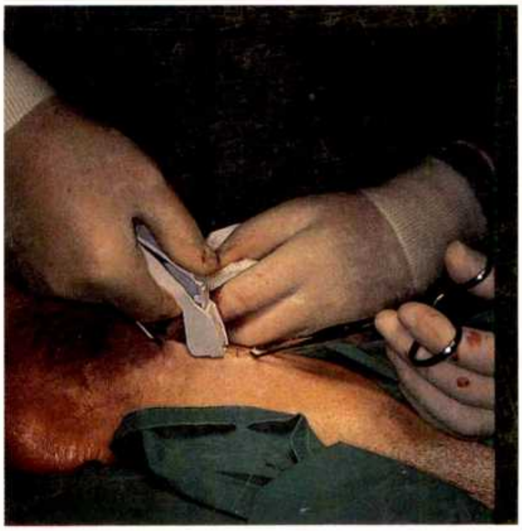

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2 Pritchard, B. and Pritchard, C. (1985) Skin staples, NATNews, July.

3 Traub, A.C. and Quattlebaum, F.W. (1981) Cutaneous Wound Closure: Early Staple Removal and Replacement by Skin Tapes. Contemporary Surgery, **Vol 18.**

4 Jewell, M.L., Sato, R. and Rahija, R. (1983) A Comparison of Wound Healing in Wounds Closed with Staples Versus Skin Suture. Contemporary Surgery, **Vol 22,** 29–32.

2 Bucknall, R.E. and Ellis, H. (1982) Skin Closure. Comparison of Nylon, Polyglycolic Acid and Staples. Euro. Surg. Res., **14,** 96–97.

6 Pickford, I.R., Bennan, S.S., Evans, M. and Pollock, A.V. (1983) British Journal of Surgery, **70,** 226.

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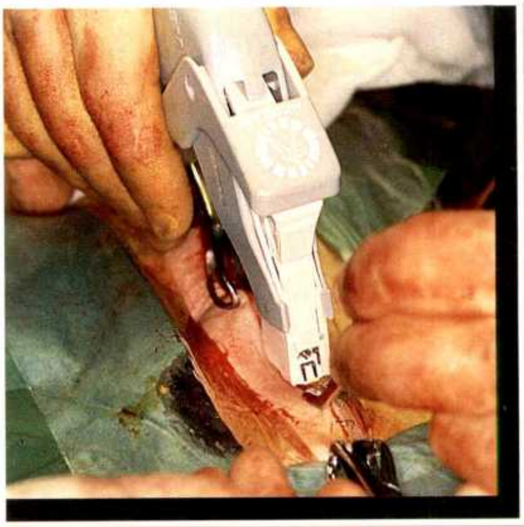

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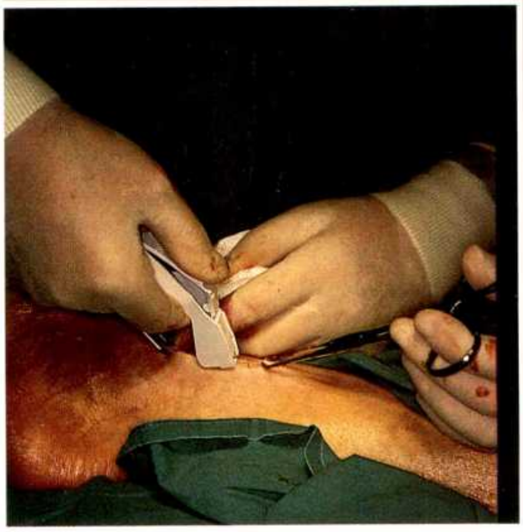

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Volume 75 Number 2 February 1988

LEADING ARTICLES

Localization studies in patients with primary hyperparathyroidism 97
N. W. Thompson
Diagnosis of pancreatic necrosis 99
M. C. Aldridge

Prospective study of conservative and operative treatment for faecal incontinence 101
R. Miller, D. C. C. Bartolo, J. C. Locke-Edmunds and N. J. McC. Mortensen
Gastric cancer: an audit of 122 consecutive cases and the results of R_1 gastrectomy 106
T. T. Irvin and J. E. Bridger
Randomized comparison of R_1 and R_2 gastrectomy for gastric carcinoma 110
D. M. Dent, M. V. Madden and S. K. Price
Tightening the loose arterial suture (surgical workshop) 112
R. L. Blackett and G. E. Heard
Experimental columnar metaplasia in the canine oesophagus 113
P. Gillen, P. Keeling, P. J. Byrne, A. B. West and T. P. J. Hennessy
A rational technique for surgical operation on Borrmann type 4 gastric carcinoma: left upper abdominal evisceration plus Appleby's method 116
H. Furukawa, M. Hiratsuka and T. Iwanaga
Isolated pyloric obstruction in association with large hiatus herniae 119
C. J. H. Ingoldby, R. Antrum and T. Gledhill
Anterior lesser curve seromyotomy with posterior truncal vagotomy *versus* proximal gastric vagotomy 121
H. J. M. Oostvogel and Th. J. M. V. van Vroonhoven
Stimulation of the healing of experimental colon anastomoses by low-power lasers 125
F. Asencio-Arana and F. Martinez-Soriano
Low molecular weight heparin compared with unfractionated heparin in prevention of postoperative thrombosis 128
M. Samama, P. Bernard, J. P. Bonnardot, Sophie Combe-Tamzali, Y. Lanson and E. Tissot on behalf of the participants of the Groupe d'Etude de l'Enoxaparine (GENOX) multicentric trial
Cytoxic-loaded albumin microspheres: a novel approach to regional chemotherapy 132
C. S. McArdle, H. Lewi, D. Hansell, D. J. Kerr, J. McKillop and N. Willmott
Wound healing response in surgical patients: recent food intake is more important than nutritional status 135
J. A. Windsor, G. S. Knight and G. L. Hill
Prediction of choledocholithiasis using a pocket microcomputer 138
T. V. Taylor, C. P. Armstrong, S. Rimmer, S. B. Lucas, J. Jeacock and A. A. Gunn
Urgent and early cholecystectomy for acute gallbladder disease 141
N. V. Addison and P. J. Finan
Non-invasive treatment for retained common bile duct stones in patients with T tube *in situ*: saline washout after intravenous ceruletide 144
R. Tritapepe, C. di Padova and F. di Padova
Anergy in jaundiced patients 147
M. Cainzos, J. Potel and J. L. Puente
Peroperative cholangiography: needle puncture of the hepatic duct *versus* cannulation of the cystic duct (short note) 149
G. T. Williams, I. S. Paterson, E. S. Kiff and M. Davies
Operative management of tubulovillous neoplasms of the duodenum and ampulla 150
Z. H. Krukowski, S. W. B. Ewen, A. I. Davidson and N. A. Matheson
Total pancreatectomy in the MEN-1 syndrome 154
L. E. Tisell, H. Ahlman, S. Jansson and L. Grimelius

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Rupture of abdominal hydatid cysts (short note) 157
C. Placer, R. Martín, E. Sánchez and E. Soleto

Pancreatitis and hyperparathyroidism 158
A. Sitges-Serra, M. Alonso, C. de Lecea, P. F. Gores and D. E. R. Sutherland

Surgery in tropical pancreatitis 161
P. G. Thomas and P. Augustine

Pancreatic trauma: acute and late manifestations 165
A. Leppäniemi, R. Haapiainen, Tuula Kiviluoto and M. Lempinen

Staphylococcus epidermidis as a cause of postoperative wound infection after cardiac surgery: assessment of pathogenicity by a wound-scoring method 168
A. P. R. Wilson, R. N. Grüneberg, T. Treasure and M. F. Sturridge

Surgical gloves as a mechanical barrier against human immunodeficiency viruses 171
A. G. Dalgleish and M. Malkovsky

Aggressive treatment of severe diffuse peritonitis: a prospective study 173
M. Schein, R. Saadia, Z. Freinkel and G. A. G. Decker

Effect of splenectomy on Gram-negative bacterial clearance in the presence and absence of sepsis 177
Sarah Cheslyn-Curtis, M. C. Aldridge, J. E. J. Biglin, J. Dye, S. J. D. Chadwick and H. A. F. Dudley

Approach to ingrowing toenails: the wedge resection/segmental phenolization combination treatment 181
M. M. Issa and W. A. Tanner

Smooth muscle tumours of the digestive tract: report of 160 cases 184
L.-J. He, B.-S. Wang and C.-C. Chen

CORRESPONDENCE 187

BOOK REVIEWS 191

NOTICES AND ANNOUNCEMENTS 192

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ATLAS OF GENERAL SURGERY ● Second Edition

Hugh Dudley ChM, FRCS(Ed), FRACS, FRCS
Professor of Surgery, St Mary's Hospital, London, UK

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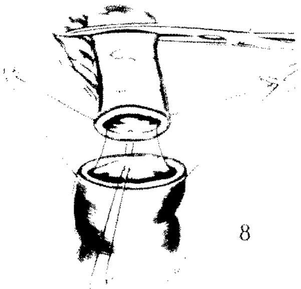

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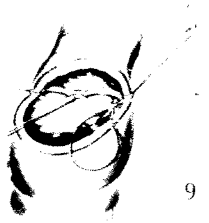

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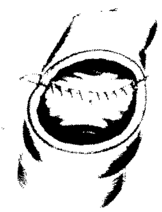

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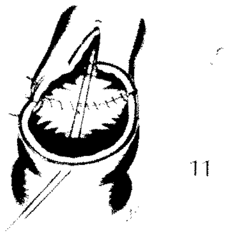

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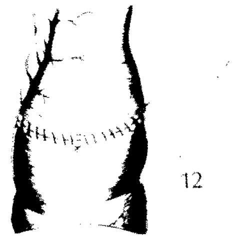

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Seventy-fifth anniversary

Last month on our cover we introduced our 75th anniversary logo. This month it appears again as a prelude to a series of the Arms of Lister and Moynihan. These will be accompanied by comments on aspects of their life and work. We consider this fitting because modern surgery and, in our country, surgical reporting rests on the shoulders of these two great men. The safety of virtually everything done technically today we owe to Lister though sometimes we forget both the scope and limitations of his thinking. More of that will become apparent during the year. As to Moynihan, his achievements embraced technical surgery, surgical education, ambassadorial activity and finally the founding of our Journal and of the Association of Surgeons. He was an extrovert, warm and gregarious but perhaps without close friends. Lister by contrast was reserved, almost a recluse, sometimes exasperating because of his chronic tardiness but always attracting loyalty to the point of hero worship.

It is fitting that we honour both in our 75th year. They will no doubt be called into prominence with greater emphasis at the time of our 100th anniversary but for now we, on the Editorial Committee of the Journal, wish to highlight them before we ourselves shuffle off this mortal coil.

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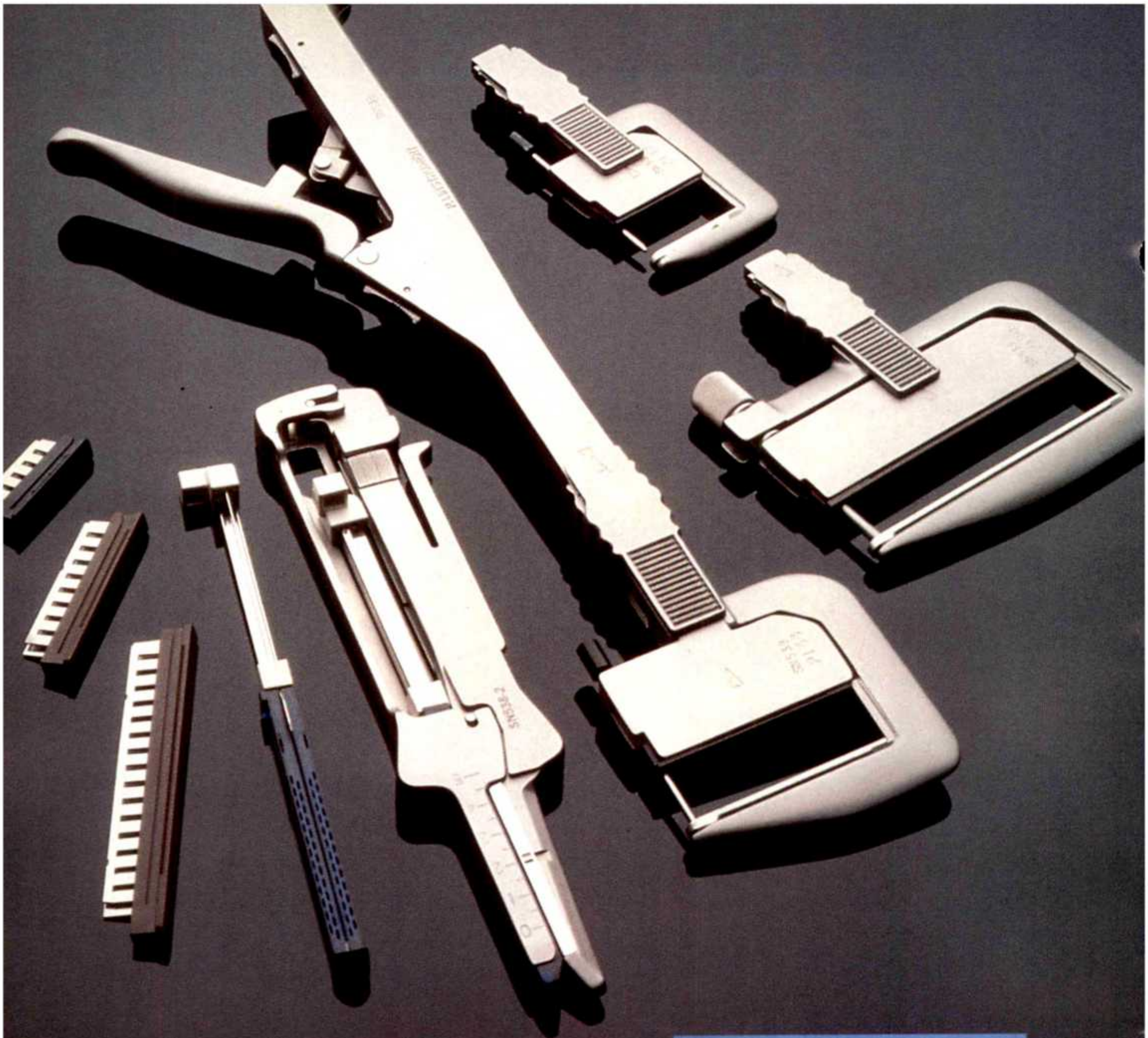

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Leading articles

Br. J. Surg. 1988, Vol. 75, February, 97–98

Localization studies in patients with primary hyperparathyroidism

Primary hyperparathyroidism (HPT) is currently the most common cause of hypercalcaemia in ambulatory patients and is second only to cancer-related hypercalcaemia in hospitalized patients. Approximately 1 in every 1000 adults have HPT and the incidence is even higher in selected population groups such as elderly women in which 1 in 200 have been found to have this disease. The apparent increase in HPT is not due to an epidemic but rather to the ability to make the diagnosis, particularly in many asymptomatic patients. The widespread use of auto-analysers which included serum calcium levels, was the real factor that exposed the high incidence of this disease in the ambulatory patients. In current series, anywhere from 10 per cent to 50 per cent of patients are considered to be 'asymptomatic'. Nevertheless, there is a developing consensus that such patients should be operated upon unless there is a compelling medical contra-indication, because there is no way of predicting who will develop complications. Furthermore, there is increasing evidence that whereas parathyroidectomy prevents complications, it does not necessarily cure them once they are established.

There has been considerable debate about the utilization of localization studies, once the diagnosis is firmly established by biochemical testing, in patients who have not been previously explored. This has intensified with the development of non-invasive studies such as ultrasonography, technetium–thallium scintigraphy, CT and MRI scanning. It is argued that the demonstration of a suspected enlarged parathyroid by these techniques confirms the diagnosis and reassures the patient, referring physician, and surgeon that the diseased gland(s) will be found and appropriately treated. A few experienced surgeons also believe that a unilateral cervical exploration is appropriate when a single enlarged gland is found at operation in addition to an ipsilateral normal gland. Although this opinion does not represent the majority view, it is an argument used in justification for pre-operative localization in patients about to undergo their first operation. It is true that the sensitivity of localization studies has improved and they are of great value when positive in planning reoperative parathyroid explorations in which anatomical changes from a previous exploration markedly increase the difficulty and the potential morbidity[1–3]. Nevertheless, localization techniques can be misleading and none alone, or in combination, compares favourably with results obtained by an experienced parathyroid surgeon carrying out a primary exploration.

At best, localization procedures will demonstrate or localize the diseased gland in approximately 80 per cent of cases. Their reliability is far less in patients with hyperplasia or multiple gland disease and in those with adenomas smaller than 1 cm in diameter. They are particularly likely to give false negative findings in patients who have asymptomatic or uncomplicated disease or in patients with kidney stones whose calcium levels may be barely above the upper range of normal. False positive studies can also mislead or misdirect the inexperienced surgeon: as an example, thallium scans may be positive in patients with a variety of thyroid lesions including medullary carcinoma and some differentiated carcinomas as well as microfollicular adenoma. The routine use of these studies in primary cases merits critical appraisal.

High-resolution ultrasonography has been found to have good specificity (95 per cent) and a sensitivity of approximately 75–80 per cent for adenomas larger than 1 cm. It is non-invasive, readily available and free of radiation. Its limitations are related to the location of adenomas; those in the retrotracheal and retro-oesophageal areas as well as in the mediastinum are usually not detected. Thyroid abnormalities, particularly multinodular goitres, decrease the sensitivity and specificity of the test. The specificity when positive approaches 95 per cent. Ultrasonography is best in demonstrating adenomas in juxtaposition to the lower pole of the thyroid gland. However, these are the easiest for the surgeon to detect at operation.

Thallium–technetium scintigraphy has a sensitivity of approximately 75 per cent and specificity of 90 per cent in primary cases. Again, thyroid abnormalities decrease the sensitivity and specificity and posteriorly located glands can be missed, regardless

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of size. However, some mediastinal adenomas can be detected, as well as some small cervical adenomas. A potential pitfall is that in some patients with hyperplasia or 'double adenomas', only one enlarged gland has been detected[4].

CT scanning has fewer advocates in primary cases because of its cost and its sensitivity of about 75 per cent. It does have the advantage of visualizing the retrotracheal and retro-oesophageal areas as well as the mediastinum. There are virtually no advocates of selective venous parathyroid hormone sampling or arteriography in the localization of parathyroid glands before a primary exploration because of their expense, invasive nature and lack of sensitivity. MRI has been found to be only 75 per cent sensitive and is also expensive.

It should be noted that most reports on the sensitivity and specificity of localization studies have come from university hospitals performing large numbers of parathyroid explorations. None, however, specifically addresses the issue of whether the experienced surgeon doing the operation was actually helped by the particular study. In as much as the experienced parathyroid surgeon is successful in finding the diseased gland(s) in 92–98 per cent of all cases, it appears unlikely that these localization studies are of any significant benefit[4].

Although many patients without previous neck explorations have been referred to our clinic in recent years with ultrasound scans and scintiscan in hand, there have been no cases in which the diseased gland(s) would not have been detected without this information. Furthermore, we have been referred a number of patients for reoperative procedures who have persistent hypercalcaemia because an inexperienced surgeon proceeded with an exploration because of a positive scan. In these cases, the surgeon did not find the diseased gland, or excised only one enlarged gland in a patient with hyperplasia or 'double adenoma'. In our opinion, all patients should have bilateral neck explorations and an attempt to identify at least four glands because of the possibilities of 'double adenomas' and/or asymmetrical parathyroid hyperplasia. In evaluating patients with primary HPT who were 65 years of age or older, we found that 9 per cent had 'double adenomas'[4]. A unilateral exploration would have failed to correct the hypercalcaemia in 5 per cent of this group. This experience reinforced our opinion that extending the operation for an average of 15 min to rule out the presence of an enlarged gland on the contralateral side was more than justified, even in the elderly[5].

Localization studies will continue to be important in patients with persistent or recurrent hyperparathyroidism. When positive, there is no question as to their value in improving reoperative surgical results. However, until a technique has been developed with a sensitivity approaching 100 per cent, their routine use before primary neck explorations is unlikely to improve results, and may do the opposite if inexperienced surgeons are encouraged to undertake the exploration. Dr John Doppman, one of the world's most experienced authorities in evaluating parathyroid localization procedures states: 'In my opinion, the only localizing study indicated in a patient with untreated primary HPT is to localize an experienced parathyroid surgeon'[2]. I am in total agreement. A careful search for all parathyroid glands based on sound embryological and anatomical knowledge, and an understanding and familiarity with their pathological conditions, remain fundamental to the success of parathyroid surgery.

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Br. J. Surg. 1988, Vol. 75, February, 99–100

Diagnosis of pancreatic necrosis

Stratification of acute pancreatitis into mild and severe forms by the criteria of Ranson[1] or Imrie[2] is well-established but has little to offer in the absence of satisfactory treatment for those patients identified as having severe disease. Medical management of severe necrotizing pancreatitis is associated with a mortality rate as high as 80 per cent, and peritoneal lavage probably has little significant effect upon survival[3]. These two forms of treatment fail to halt the progression of pancreatic parenchymal necrosis, the extent of which correlates significantly with mortality[4] and determines the clinical course in acute pancreatitis[5]. Excision of all necrotic pancreatic tissue would therefore seem logical. Recent reports[6–8] appear to support this hypothesis, reducing mortality rates to between 30 and 40 per cent. Central to such management is an accurate means of detecting pancreatic necrosis and its extent.

There are no specific clinical features which indicate the presence of pancreatic necrosis and indeed physical signs such as a pyrexia $>38°C$, abdominal distension with rigidity, ileus, and an abdominal mass do not correlate with the extent of gland necrosis[9]. Nordback and co-workers[9] found that leucocyte count, platelet count, haematocrit, blood glucose concentration and serum levels of sodium, potassium, calcium, triglycerides, creatinine, bilirubin and transaminases all failed to correlate with the extent of parenchymal necrosis in surgically resected glands. Furthermore, the macroscopic appearance of the pancreas at operation correlated poorly with the extent of necrosis determined histologically[9].

In an effort to find a single, reproducible blood test to detect pancreatic necrosis a number of serum factors have been investigated. These include poly-[C]-specific ribonuclease (RNAase), α-protease inhibitor, α_2-macroglobulin, complement factors C_3 and C_4, and C-reactive protein. RNAase is released from cell breakdown in the anoxic pancreas and Warshaw and Lee[10] measured this enzyme in 38 patients with acute pancreatitis. In those with normal levels there was a 4 per cent incidence of pancreatic necrosis whereas necrosis was present at operation in 11 of 13 patients in whom RNAase values were elevated.

The antiproteases α_1-protease inhibitor and α_2-macroglobulin have a protective role in binding to trypsin should trypsinogen become prematurely activated. The α_1-protease inhibitor is an acute phase reactant which rises sharply in acute pancreatitis whereas levels of α_2-macroglobulin fall with increasing severity[11]. Buchler and colleagues[12] assayed both antiproteases in 35 patients with acute pancreatitis and correlated levels with the presence or absence of pancreatic necrosis as defined histologically in the resected pancreas or on CT scanning. Levels of α_1-protease inhibitor correctly predicted necrosis in 77 per cent of cases whereas α_2-macroglobulin did better at 85 per cent.

The role of C_3 and C_4 in predicting severity is unclear. Plasma levels of both components are reduced during the acute attack and Foulis and colleagues[13] found that low levels persisted in patients who died from severe haemorrhagic pancreatitis but returned to normal in survivors. In a prospective study[12] levels of C_3 and C_4 were persistently depressed in patients with pancreatic necrosis and the overall detection rate for necrosis was 74 per cent for C_3 and 79 per cent for C_4.

The serum factor which may prove most useful, both in terms of its accuracy in the prediction of complications and its simplicity of assay, is the acute phase protein C-reactive protein. Mayer and co-workers[14] found that a level of C-reactive protein above $75\ \mathrm{mg\,l^{-1}}$ accurately predicts severity, while Buchler and colleagues[12] have reported a 95 per cent accuracy in detection of necrosis if levels exceed $100\ \mathrm{mg\,l^{-1}}$.

The imaging methods evaluated in the diagnosis of pancreatic necrosis are ultrasonography, ^{111}indium-labelled leucocyte scanning and CT. Ultrasound is unhelpful for two reasons. Firstly, over 20 per cent of examinations fail because of overlying bowel gas[12]. Secondly, when necrosis occurs ultrasound has a low sensitivity in differentiating liquid collections from necrotic parenchmya[15]. ^{111}Indium-labelled leucocyte scanning has a similar accuracy to prognostic factor grading in the assessment of severity but is poor at distinguishing between necrosis and pancreatic abscess[16].

In 22 patients with surgically proven pancreatic necrosis, White and colleagues[17] found that in its early stages, the CT appearance of necrosis was indistinguishable from that of a pancreatic phlegmon[18] but that in the subacute and chronic stages (10 days from the onset of the attack) necrosis gave a typical CT appearance which included diffuse enlargement of the gland, decreased central density and a thick rim producing a sac-like configuration. Kivisaari and co-workers[19] recommend the use of contrast-enhanced CT (CE–CT) in the early diagnosis of necrosis. Intravenous contrast fails to enhance the pancreas in patients with necrosis whereas higher density values are obtained in those with inflamed but viable pancreatic tissue. Recently, Block and colleagues[20] compared pre-operative CE–CT, ultrasound and Ranson's criteria in the diagnosis of pancreatic necrosis in 77 patients who underwent resection. CE–CT was superior to the other two methods, identifying 90 per cent of the cases with extensive necrosis (50–100 per cent of the gland) and 79 per cent of those with minor necrosis.

Once pancreatic necrosis has been diagnosed, the surgeon is still faced with the decision of when to operate. Should this decision be influenced simply by the extent of necrosis? Recent evidence suggests that the presence of bacterial contamination of necrosis should be the deciding factor. Gerzof and co-workers[21] and more recently Beger and colleagues[22] have demonstrated that bacterial super-infection occurs early (24 per cent infected during the first 7 days of the attack[22]) and causes a significant increase in mortality (37·8 per cent in infected necrosis and 8·7 per cent in sterile necrosis[22]). CE–CT appears to be the most accurate method of imaging pancreatic necrosis and, when used in conjunction with bacteriological examination of material obtained by percutaneous fine needle aspiration, may provide the surgeon with what up until now has been lacking in this difficult condition—namely definitive indications for operation.

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Br. J. Surg. 1988, Vol. 75, February,
101–105

Prospective study of conservative and operative treatment for faecal incontinence

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To assess the functional results of treatment of faecal incontinence we carried out physiological and radiological measurements in 46 patients and 20 controls. Twenty patients were selected for conservative treatment and 26 for surgery (including 17 postanal repairs and 6 anterior sphincter repairs). The degree of incontinence was scored before and after treatment and postoperative investigations carried out on 17 patients (11 postanal repairs). Forty per cent of the conservative treatment group had a successful result compared with sixty-five per cent of the operative group as a whole and fifty-nine per cent of the postanal repair patients. Resting and 'squeeze' anal canal pressures were improved following postanal repair as was upper anal canal sensation but there was no change in the anorectal angle. We conclude that the anorectal angle is not crucial in maintaining continence.

Keywords: Anorectal incontinence, postanal repair, treatment

A number of factors have been suggested as being important in maintaining anorectal continence[1–12], in particular the puborectalis sling and the angulation that it produces between the axis of the rectum and anal canal has been emphasized[1,3]. Continence is maintained according to this theory, by the anterior rectal wall being driven down into the upper anal canal by increases in the intra-abdominal pressure creating a 'flap-valve' effect. Several authors have described an obtuse angle in patients with idiopathic faecal incontinence[1,3,5,13,14] and the operation of postanal repair introduced in 1959 was specifically designed to correct this angle by creating a lattice across ileococcygeus and pubococcygeus and by tightening the puborectalis muscle behind the rectum[5]. Excessive straining at stool and obstetric injury probably results in perineal descent and traction neuropathy of the nerve supply to the pelvic floor and anal sphincter[1,15]. The aim of this study was to assess prospectively the results of conservative and surgical treatment of faecal incontinence, and in particular the effect of postanal repair on physiological and radiological tests of function in an attempt to provide a rational basis for surgery.

Patients and methods

A total of 56 patients were referred with incontinence over the study period from 1983 to 1986 of which 46 are reported here. The remaining ten patients (seven postanal repairs, two anterior sphincter repairs, one conservative) had not completed their postoperative studies at the time of writing. Patients with incontinence following surgery were excluded. A group of 20 healthy patients with no anorectal complaints served as controls. Patient details are given in *Table 1*.

Clinical assessment

Each patient was assessed clinically and the degree of incontinence was scored on a scale of 1 to 18. Three grades were assigned to the frequency of incontinent episodes:

Grade I—incontinence less frequent than once a month.
Grade II—incontinent episodes between once a month and once a week.
Grade III—incontinent episodes more than once a week.

Continence to flatus, fluid and solid stool was assessed using these grades and a score given for each, the magnitude of which reflected increasing severity of incontinence both in terms of frequency and the nature of the incontinent episode (*Table 2*). General physical examination included a limited neurological examination of the lumbrosacral plexus, a digital rectal examination, sigmoidoscopy and proctoscopy. Physiological and radiological studies were performed on a separate day.

Manometry

The manometric system consisted of a water-filled 6 mm microballoon catheter connected via non-distensible tubing to an external transducer (Statham P23 Gb, Waltham, Massachusetts, USA) and the pressure recorded on a multichannel pen recorder (Hewlett-Packard, Waltham, MA, USA). The sphincter length (length of high pressure zone), maximum resting pressure and maximum voluntary contraction ('squeeze') pressure were measured by a standard station pull-through technique[11].

Anal sensation and electromyography

The length of the anal canal as defined by manometry was divided into three equal zones and the anal mucosal electrosensitivity in each zone was assessed using a special catheter carrying two platinum electrodes 1 cm apart. Three patients in this study had sphincters that measured 2 cm or less and in these patients measurements of sensitivity could only be assessed in the upper and lower halves. A small electric current from a constant current generator (Department of Medical Physics, Bristol Royal Infirmary, Bristol, UK) was passed between the electrodes until the patient perceived a sensation often described as a tingling or tapping. An average of three recordings at each level was taken as the threshold value. The method has been described in detail in a previous publication[11]. A standard electromyograph (EMG) apparatus (Type

Table 1 *Age and sex of patient groups*

Patients	*n*	M:F	Age
Controls	20	8:12	59·5 (30–83)
Incontinent			
Conservative	20	5:15	67 (37–80)
Operative	26	0:26	60 (26–88)

Table 2 *The incontinence score system*

Grade	Flatus	Fluid	Solid
I	1	4	7
II	2	5	8
III	3	6	9

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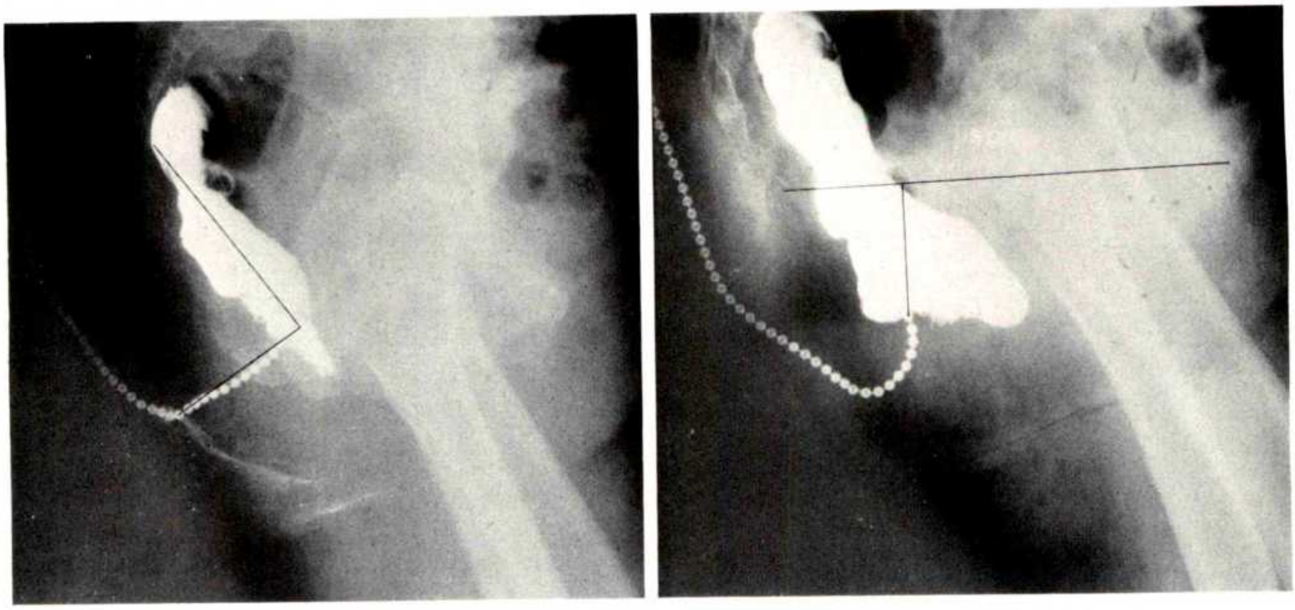

Figure 1 *Proctograms showing measurements of anorectal angle and perineal descent*

MES, Medelec, Woking, UK) with a conventional concentric needle (Type 13L49, DISA, Copenhagen, Denmark) was used in selected cases to confirm the clinical findings of a gap in the external anal sphincter.

Radiology

The anorectal angle was measured radiologically by the technique described previously[13]. Lateral radiographs were taken with the subject at rest, during a voluntary contraction and whilst straining as at stool (*Figure 1*). In brief, the rectum was outlined with 50 ml of dilute barium and the anal canal delineated by a row of metal beads attached to a small wooden ball placed in the rectum. The angle between the axis of the rectum, and the anal canal as delineated by the beads, was defined as the anorectal angle. Perineal descent was measured from the highest bead in the anal canal to the plane of the perineum, defined as the line joining the most anterior portion of the symphysis pubis with the lowermost portion of the coccyx.

Treatment selection

Patients were selected for conservative or operative treatment on the basis of both clinical and physiological information. For example, if the patient gave a history of a third degree tear in pregnancy and had a gap in the sphincter clinically which was confirmed on EMG, then an anterior sphincter repair was recommended; six patients had this procedure. Seventeen patients had idiopathic faecal incontinence with severe symptoms, low sphincter pressures and no obvious cause of their incontinence. They were treated by postanal repair. Two patients had rectal prolapse and incontinence despite good sphincter pressures and had an abdominal rectopexy with ivalon sponge. One patient with both rectal prolapse and poor sphincter function had a combined rectopexy and postanal repair. All patients had a clinical assessment after treatment and 17 operated patients (including 11 postanal repairs) had physiological and radiological investigations postoperatively.

The remaining 20 patients were treated conservatively. None had any obvious cause for their incontinence; in particular no neurological or obstetric factor could be implicated. Incontinence in this group was in general less severe, 45 per cent being continent to solid stool as compared with only 4 per cent of the operative patients. They tended to be older than the operative group and their incontinence was often associated with a loose stool. In a few patients surgery was the treatment of choice but was precluded by their poor general health.

Treatment

Conservative treatment commenced with counselling and advice on the mechanism of continence. Constipating agents such as codeine phosphate or loperamide were usually prescribed and some patients used glycerin suppositories every morning to empty the rectum in an attempt to prevent soiling later in the day. They were also advised to refrain from eating a high fibre diet and specific high fibre supplementation was stopped. We have not found physiotherapy or pelvic floor faradism to be of any benefit and do not use them. In one patient cholestyramine was used to reduce diarrhoea.

Surgery was carried out by one surgeon (N.M.) after bowel preparation with Picolax (Nordic, Feltham, UK) and antibiotic prophylaxis was used (three perioperative doses of cefuroxime and metronidazole). Anterior sphincter repair was similar to that described by Parks and McPartlin[16] using a nerve stimulator to locate the cut and retracted ends of the external anal sphincter. The ends were overlapped and sutured with interrupted 2/0 Prolene (Ethicon, UK). Postanal repair was performed with the patient in the lithotomy position, catheterized and the buttocks strapped apart. A V shaped postanal incision was made and a skin flap raised anteriorly to expose the external anal sphincter. Adrenaline was infiltrated into the intersphincteric plane and dissection continued in this plane. At the top of the sphincter apparatus Waldeyer's fascia was identified and divided and the rectum pushed anteriorly to enable ischiococcygeus and puborectalis to be plicated behind the rectum with interrupted 2/0 Prolene sutures. Unlike Parks' original description, no lattice was made across the ileococcygeus or pubococcygeus. The same suture material was used to imbricate the external anal sphincter except in the most superficial region just beneath the skin where 2/0 Vicril (Ethicon, UK) was used. A Redivac drain (OEC Orthopaedic Ltd, Bridgend, UK) was inserted and the wound was closed by a limited V–Y plasty procedure. Covering stomas were not used for either anterior sphincter or postanal repair.

The conservative group were followed-up for a median of 14 months (range 4–33), anterior sphincter repairs for 13 months (range 7–24) and the postanal repairs for 15 months (range 3–40). Ethical Committee approval was given for the study by the Bristol and Weston Health Authority.

Statistical analysis

A Kruskal–Wallis one way analysis of variance for non-parametric data was first carried out and then the Mann–Whitney U test used to compare individual groups. To compare pre-operative and postoperative data in the postanal repair group the patients acted as their own controls and a Wilcoxon paired signed-ranks test was applied.

Results

In general the patients who had an anterior sphincter repair tended to be younger and have fewer symptoms than either the idiopathic or conservatively treated group (*Tables 1* and *3*). The conservative group had a milder degree of incontinence before commencement of treatment (*Table 3, Figure 2*). The median sphincter length in the controls was 3·75 cm and this was significantly reduced in the incontinent patients (3 cm in both conservative and operative groups, $P < 0{\cdot}01$). Maximum resting pressure (MRP) and maximum voluntary contraction (MVC) pressure were also reduced in the incontinent patients (*Table 4*). This reduction in sphincter function was more pronounced in the operative group (MRP conservative 67 cmH_2O *versus* operative 42 cmH_2O, $P<0·05$; MVC conservative 145 cmH_2O *versus* 82 cmH_2O, $P<0·05$). There was also an impairment of mucosal electrosensitivity in the operative group similar to that which we have previously described ($P<0·001$ at all levels of the anal canal)[11]. In the conservative group, only the upper zone of the anal canal was relatively insensitive ($P<0·01$). There was no difference in electrosensitivity between the controls and the conservative group in the middle and lower zones of the anal canal. Radiological investigations did not reveal any difference in anorectal angle between the controls and either conservative or operative groups, neither was there any difference apparent if the idiopathic group alone was compared with the controls. There was a significant increase in perineal descent at rest, squeeze and strain positions between controls and the conservative group ($P<0·05$) and controls and the operative group ($P<0·001$).

A successful outcome of treatment was defined as a 75 per cent reduction in the patients' pretreatment incontinence score. In practice this meant that our patients had no soiling episodes at all and at worst were only incontinent to flatus The patients who had an anterior sphincter repair had the best result with 83 per cent being classified a success. The idiopathic group who had a postanal repair were successful in 59 per cent, and conservative management was successful in only 40 per cent of cases (*Figure 2*).

In the patients treated by postanal repair the MRP and

Table 3 *Clinical details from patient groups*

	Conservative ($n=20$)	Anterior sphincter repair ($n=6$)	Postanal repair ($n=17$)
Age	67 (37–80)	40 (27–67)	62 (39–88)
Duration of symptoms (months)	24	18	36
Follow-up (months)	14	12	15
Incontinence score median (range)	13·5 (5–18)	18 (16–18)	17 (8–18)
Straining	25%	16%	36%
Call to stool	90%	100%	100%
Urgency	60%	16%	59%
Perineal pain	15%	0%	0%
Prolapse	5%	0%	6%
Pruritus	10%	0%	18%
Deliveries per patient	1·6	2	2·7
Hysterectomy	30%	33%	35%
Perineal tears per delivery	31%	100%	59%

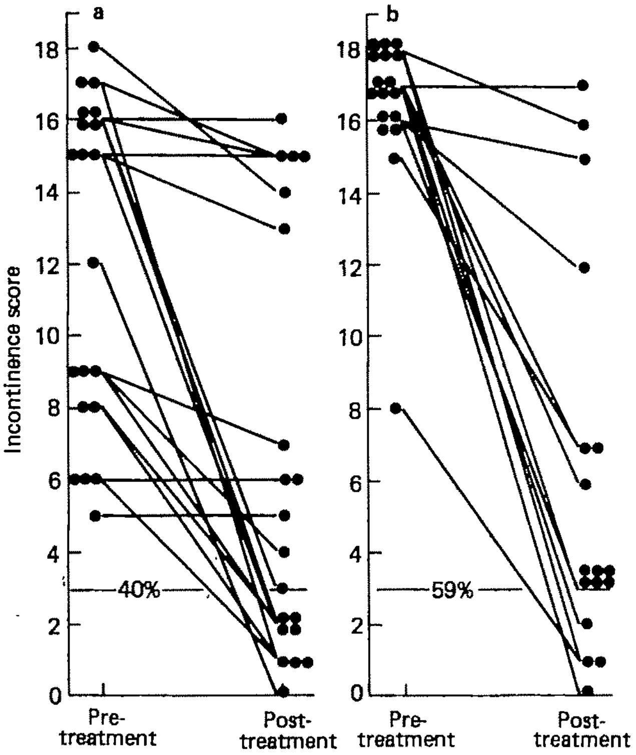

Figure 2 *Results of pre- and post-treatment incontinence scores in the* **a** *conservative and* **b** *postanal repair groups. Forty per cent of conservatively treated patients were defined as having a successful result compared with 59 per cent of postanal repairs*

Table 4 *Results of pretreatment investigations compared with controls*

	Controls ($n=20$)	Conservative ($n=20$)	Total operative ($n=26$)	Anterior sphincter repair ($n=6$)	Postanal repair ($n=17$)
Sphincter length (cm)	3·75	3^a	3^a	$2·8^a$	3^a
Maximum resting pressure (cmH_2O)	105	67^a	$42^{b,d}$	45^a	40^b
Maximum voluntary contraction (cmH_2O)	227	145^b	$82^{b,d}$	75^a	80^b
Anal canal electrosensitivity (mA)					
Lower	4·8	5·6	$6·6^b$	5·6	$7·0^a$
Middle	4·0	4·0	$6·3^b$	$7·0^a$	$6·2^a$
Upper	5·6	$8·0^a$	$11·5^b$	$9·6^a$	$12·6^b$
Anorectal angle					
Rest	92	100	97	100	97
Squeeze	86	91	84	84	83
Strain	111	108	110	120	107
Perineal descent					
Rest	0	$-1·4^b$	$-1·2^a$	$-0·5$	$-1·2^b$
Squeeze	1·0	$-1·1^c$	$-1·1^a$	$-0·6^c$	$-0·9^b$
Strain	$-1·7$	$-4·5^a$	$-4·4^b$	$-4·0^c$	$-4·3$b

[a,b,c] Significant difference from controls $P<0·01$, $<0·001$, and $<0·05$ respectively
[d] Significant difference from conservative group $P<0·05$

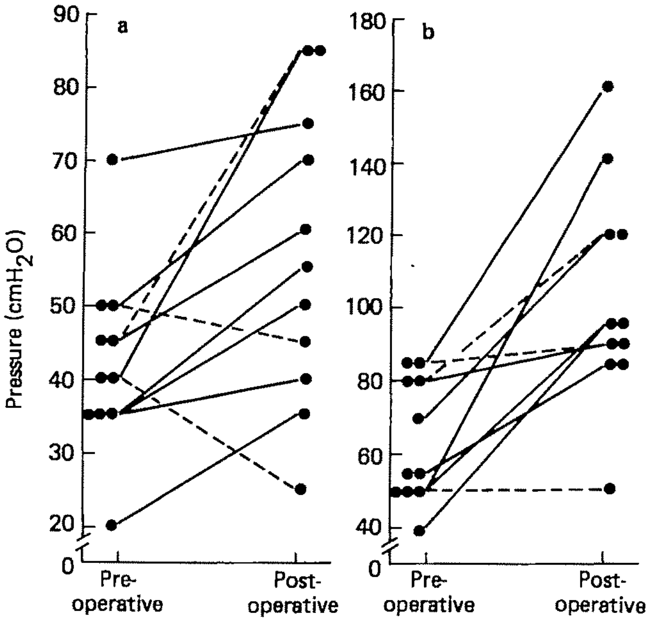

Figure 3 *Pre- and postoperative* **a** *maximum resting and* **b** *maximum voluntary contraction pressures in the postanal repair group. Both pressures increased following surgery,* $P<0.05$ *and* <0.01 *respectively. Broken line represents a poor result (less than 75 per cent improvement in their pre-operative score)*

MVC sphincter pressure increased after surgery (*Figure 3*) ($P<0.05$ and <0.01 respectively). Anal sensation assessed by mucosal electrosensitivity improved in the upper zone of the anal canal from a pre-operative median of 13·6 to 7 mA postoperatively ($P<0.05$). An improvement was recorded in upper anal electrosensitivity in six of the eight patients who had a successful result. One patient in this group had no change in sensation and another had a small rise in sensory threshold from 15 to 19 mA. Of the three failed postanal repairs studied, two had either no change or a reduction in upper anal sensation and one had an improvement.

There was no change in the anorectal angle following postanal repair in any of the three positions of rest, squeeze or strain. This was also true if those patients who had a poor result were excluded from the analysis. The only other factor which was changed by the operation of postanal repair was the degree of perineal descent at rest, which increased after surgery from a pre-operative median of −0·5 to −1·2 cm. Full details of the pre- and postoperative investigations in 11 of the 17 patients who had a postanal repair are given in *Table 5*. Postoperative complications were negligible. No patient developed a wound infection and the wound healed by first intention in almost all cases.

Discussion

Of the many factors that have been suggested as having a part to play in maintaining continence obviously the anal sphincters which are continuously and reflexly active even during sleep[7,8] have a primary role, but whether this is due to a simple pressure barrier or resistance to stretch is disputed[9]. An additional characteristic of muscle function that may aid continence is the reverse gradient of activity which has been demonstrated in both the sigmoid colon[10] and the anal canal[17] which in theory may slow the passage of stool and clear the anal canal of faeculent debris and so prevent soiling. Our findings, in common with many others, have demonstrated a reduction in the power of the anal sphincter as measured by the MRP and MVC. Several studies have correlated a rise in the MRP with successful results following postanal repair in particular[18,19]. Our results confirm this finding but in addition we demonstrated a rise in the MVC. This is similar to results described by Browning and Parks[18] but differs from those of Keighley and Fielding[19]. The importance of the resting tone of the anal sphincters was emphasized by Snooks *et al.*[20] when they analysed a group of failed postanal repairs and found that the resting pressure in this group was not improved by surgery. It is interesting to note that in two of our three failures, who had postoperative studies, their resting pressure fell postoperatively and there was no significant improvement in their MRPs (*Figure 3*). Pre-operative sphincter length as measured by manometry was shorter in the incontinent patients but unlike others[18,21] we found no increase in sphincter length following postanal repair.

Sensory factors are also likely to have an important role in maintaining continence. Goligher felt that a rectal stump of at least 6 cm should be left when resecting rectal tumours to preserve rectal sensation[5]. It was possible to preserve the sphincters and yet in some cases have poor functional results following a low anastomosis. After pull-through procedures in which the mucosa was sacrificed clinical results were worse than in those cases where the mucosa was left intact. It is now clear however that the sensation of rectal fullness is still present following complete excision of the rectum and a colo-anal anastomosis[21], suggesting the presence of receptors in the pelvic floor. In addition the anal canal is also involved in the sensory part of the continence mechanism. It has a profuse sensory innervation[22]. During the sampling reflex[12] this specialized epithelium comes into contact with rectal contents so helping to distinguish between gas, liquid and solid. In this study we found a significant improvement in upper anal canal sensation following postanal repair. This is objective evidence confirming the frequent statements from patients that after such surgery they are more aware of rectal contents and impending 'accidents' and are therefore more able to take precautionary measures. The reason for this improved sensation is not clear. A possible explanation is that surgery may pull the sensitive mucosa higher up the anal canal and so increase its contact with rectal contents. In this study the length of the high pressure zone was unchanged by postanal repair so that the differences in sensation cannot be accounted for by differences in the distance from the anal verge at which sensation was tested.

Although several authors have shown a more obtuse anorectal angle in idiopathic faecal incontinence[1,3,13] we cannot

Table 5 *Results of pre-operative versus postoperative investigations in 11 patients in the postanal repair group*

	Pre-operative	Postoperative	*P* value
Sphincter length (cm)	3	3	n.s
Maximum resting pressure (cmH_2O)	40	50	<0·05
Maximum voluntary contraction (cmH_2O)	55	95	<0·01
Anal electro-sensitivity (mA)			
Lower	6·6	8·0	n.s.
Middle	6·3	7·0	n.s.
Upper	13·6	7·0	<0·05
Anorectal angle			
Rest	95	93	n.s.
Squeeze	84	75	n.s.
Strain	109	98	n.s.
Perineal descent (cm)			
Rest	−0·6	−1·2	<0·05
Squeeze	−0·7	−1·3	n.s.
Strain	−2·9	−4·1	n.s.

Values are medians; n.s., not significant confirm this. There was a slight trend to a wider angle in our patients with idiopathic faecal incontinence and it is possible that with a larger group this may have reached significance. A reduction in the anorectal angle after postanal repair has also been reported[3] but our study did not demonstrate any improvement. Again there was a trend to a more acute angle postoperatively but this did not reach statistical significance. These findings cannot be explained on the basis of differences in the age or sex distribution in patient groups or on the overall outcome of surgery as these factors are similar in each study. Womack *et al.*[23] recently reported similar findings in a group of 14 patients undergoing postanal repair. In more than one-third of their patients the pre-operative anorectal angle was within the normal range and in the group as a whole the anorectal angle was not significantly different following surgery. Further evidence that questioned the flap-valve theory of continence was provided by Bartolo *et al.*[24] using video-proctography to study the anorectal morphology during a Valsalva manoeuvre. At no time during this procedure was the rectal wall seen to be in contact with the upper anal canal, continence being maintained by sphincteric action alone.

Reports of the degree of success following postanal repair are similar[19,25]. Continence to solid and liquid stool is achieved in 58–63 per cent of cases and our result of 59 per cent is in accord with this. Conservative treatment was disappointing. Keighley and Fielding[19] reported only 16 per cent of patients maintaining long-lasting benefit with anti-diarrhoeal agents and 15 per cent following physiotherapy. In this study 40 per cent had a successful outcome at the median follow-up period of 14 months. Only 10–20 per cent of these patients continued taking their medication for more than 1 month. It appeared that a proportion of these patients were referred with transient incontinence associated with an isolated episode of diarrhoea, which would have resolved spontaneously as the diarrhoea settled. An additional factor was the intermittent nature of their symptoms with periods of continence often being followed by long periods of near normal continence during which time no medication was necessary. They appeared, as Keighley and Fielding commented[19], to be 'satisfied with the results of conservative therapy' although classified as failures by the scoring system.

Our results demonstrate that the majority of patients are improved by surgery for incontinence and that current conservative therapy is less successful. The success of surgery is related more to an improvement in sphincter pressures and anal sensation than to any effect on the anorectal angle.

Acknowledgements

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Gastric cancer: an audit of 122 consecutive cases and the results of R_1 gastrectomy

In a consecutive series of 122 patients with gastric carcinoma, 9 per cent had no operation, 27 per cent had incurable disease at laparotomy, and 64 per cent underwent gastric resection. R_1 gastrectomy was performed in 73 of the 78 resections. The operative mortality after gastric resection was 4 per cent, but there were no deaths after potentially curative resections. The actuarial 5-year survival was 20 per cent overall, 60 per cent in patients undergoing a 'curative' resection with N_0 disease, and 18 per cent in patients with N_1 disease. Local or regional recurrence without evidence of distant metastases was identified in 11 per cent of cases after 'curative' resections. The probability of survival was adversely affected by N_1 nodal involvement ($P<0{\cdot}005$) *and by the presence of poorly differentiated or anaplastic tumours* ($P<0{\cdot}001$). *Only 6 per cent of patients had early gastric cancer, and absolute curative resections by Japanese criteria were possible in only 5 per cent of cases. The results suggest that the unfavourable presenting pathology is the principal determinant of the poor prognosis of gastric cancer. A more radical or extended lymphadenectomy ($R_{2/3}$ gastrectomy) might have cured more patients with N_1 metastases, but only 12 per cent of potentially curable patients had N_1 disease in this study, and it appears that more radical surgery may have little effect on the overall survival rates for gastric cancer.*

Keywords: Gastric cancer, gastrectomy

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Gastric cancer has a much better prognosis in Japan than in Europe or the USA[1,2]. Much of this difference may be explained by earlier detection of the disease in Japan[1], but it has been suggested that the difference is also due to the use of more radical methods of gastric resection[3–5]. The R_2 and R_3 types of gastrectomy are routinely used in most operations for gastric cancer in Japan and, depending on the location of the primary growth, they include the removal of coeliac, juxtapyloric, retroperitoneal, peripancreatic, and perisplenic (N_2N_3) lymph nodes as well as the perigastric (N_1) nodes. This contrasts with the surgical practice in the UK and USA where the R_1 gastrectomy predominates and only the perigastric (N_1) lymph nodes are removed in a gastric resection[6]. Western resistance to the use of more radical types of gastrectomy is explained by uncertainty regarding the value of such procedures and by the unfavourable results of such operations in the USA 20 years ago[7].

We have reviewed our recent experience of 122 consecutive cases of gastric cancer and the results of the R_1 gastrectomy. Using this clinicopathological data we have also assessed the potential value of extended lymphadenectomy in the $R_{2/3}$ types of gastrectomy.

Patients and methods

One hundred and twenty-two patients referred to our unit with histologically proven carcinoma of the stomach during the period 1979–1986 form the basis of this study. The group comprised 73 men and 49 women of average age 71 years (range 33–90 years), and all patients were followed up until death or annually to the date of the review. The average duration of the follow-up was 4·4 years (range 1–8 years)

The clinical extent of the disease at laparotomy was carefully documented with regard to the presence of serosal involvement, the extent of nodal metastases, and the presence of hepatic or peritoneal metastases. Histopathological evaluation of the tumours in resected specimens included a description of tumour morphology and size, the differentiation and depth of invasion of the growth, the margins of clearance in resections, and the extent of nodal involvement. Using such data it was possible to stage the tumours according to the general rules of the Japanese Research Society for gastric cancer (*Table 1*)[8], with the exception of nodal metastases. In the majority of cases in this study the N_{2-4} nodes were not resected, and the histological evaluation of nodal metastases was confined to the N_1 or perigastric lymph nodes.

Age-adjusted actuarial survival curves were constructed for different clinical and pathological variables[9–11], and statistical comparisons made using the log rank test[12].

Results

Treatment

It was the policy of this unit to resect the primary tumour whenever possible. However, 11 patients (9 per cent) had no surgical treatment either because of very advanced disease (4 patients), or because they were medically unfit (6 patients), or

Table 1 *Staging of gastric cancer according to the general rules of the Japanese Research Society*

Stage	Peritoneal metastases	Hepatic metastases	Lymph node metastases	Serosal involvement
I	P_0	H_0	N_0	S_0
II	P_0	H_0	N_1N_2	S_1
III	P_0	H_0	N_3	S_2
IV	$>P_1$	H_1	N_4	S_3

P_0, no peritoneal involvement; P_1, involvement of adjacent peritoneum; H_0, no hepatic metastases; H_1, hepatic metastases; N_0, no nodal involvement; N_1, involvement of perigastric nodes; N_2, involvement of coeliac axis nodes; N_3N_4, involvement of hepatoduodenal, retropancreatic, mesenteric and para-aortic nodes; S_0, no serosal involvement; S_1, suspected serosal involvement; S_2, definite serosal involvement; S_3, involvement of other organs

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Table 2 *Extent of residual malignancy in 41 palliative resections*

Extent of residual malignancy	No. of cases (%)
Incomplete removal of S_3 growth	19 (46)
Massive $N_{2/3}$ involvement	32 (78)
N_4 involvement	3 (7)
Diffuse peritoneal metastases	5 (12)
Hepatic deposits	3 (7)

Table 3 *Thirty-day hospital mortality. There were no deaths after potentially 'curative' gastric resection*

	No. of cases	Hospital deaths (%)
All patients	122	11 (9·0)
Surgical resection	78	3* (3·8)
No resection	33	7† (21·2)
No operation	11	1 (9·1)

* 3 deaths after palliative resection; † significantly higher mortality in non-resectional surgery compared with gastric resection (Fisher's exact test $P = 0.014$)

because they refused surgery (1 patient). Thirty-three patients (27 per cent) had irremovable tumours at laparotomy, and a palliative oesophageal intubation or gastrojejunostomy was performed in 16 cases. A gastrectomy was performed in 78 patients (64 per cent), and in 73 cases this was an R_1 resection removing part or all of the stomach, omenta, and the perigastric (N_1) lymph nodes. Five patients underwent an R_2 or R_3 gastrectomy *de necessitate* for tumours involving the pancreas or posterior abdominal wall. The 78 resections included distal partial gastrectomy in 37 cases, proximal partial gastrectomy in 18 cases, and total gastrectomy in 23 cases.

Based on clinicopathological data, the gastric resection was judged to be 'radical' or potentially curative in 37 patients (30 per cent): these patients had no evidence of peritoneal (P_0) or hepatic metastases (H_0); serosal involvement was either absent (S_0), suspected (S_1) or present (S_2); and there was no clinical evidence of nodal involvement extending beyond the perigastric (N_1) nodes. Early gastric cancer occurred in seven patients with disease confined to the mucosal or submucosal layers of the stomach. However, histological evidence of N_1 involvement was present in 15 of 37 cases of 'radical' resections. The Japanese definition[8] of a 'radical' or curative resection differs from these criteria: an 'absolute curative' resection in Japan requires that there are no peritoneal or hepatic deposits; there is no serosal involvement; and the resection must include a tier of uninvolved lymph nodes beyond that containing metastases. The Japanese also recognize a category of 'relative curative' resection which differs only in that the resection level equals the level of nodal involvement. Using these definitions, the 37 'radical' resections in the present study can be reclassified as follows: 6 were absolute curative; one was relative curative; and 30 were relative non-curative. Thus, only 5 per cent of the 122 patients had an absolute curative operation by Japanese standards.

The clinical extent of the residual disease in 41 palliative resections is documented in *Table 2*. The extensive nature of the disease in these patients was confirmed by histology, and in 10 cases there was also histological evidence of disease at the lines of resection in gastrectomy specimens.

Hospital mortality

The 30-day mortality for the entire group was 9 per cent, and the majority of hospital deaths occurred in patients with irremovable tumours (*Table 3*). The mortality in this group (21 per cent) was significantly greater than that encountered after gastric resection (4 per cent). Three deaths occurred after palliative proximal gastric resections, but there were no deaths after distal partial gastrectomy or total gastrectomy.

Survival

The age-adjusted actuarial survival curve for the entire group revealed a very high mortality in the first year but smaller numbers of deaths occurred at intervals up to 5 years after surgery (*Figure 1*). The overall 5-year survival rate was 20 per cent.

Local recurrence

Four (11 per cent) of the 37 patients undergoing a 'radical' gastric resection developed proven local or regional recurrence of the disease without evidence of distant metastases. Two patients had gastric stump recurrences after partial gastrectomy confirmed by biopsy, and two patients had CT scan evidence of recurrent disease in the posterior abdominal wall or porta hepatis (one partial gastrectomy; one total gastrectomy). All four cases had N_1 nodal involvement at the original operation.

Prognostic factors

Various subgroups of patients were examined to determine the effects of different clinical and pathological variables on survival.

Tumours involving the proximal stomach were associated with a rather lower survival rate than tumours of the antrum (*Figure 2*) but the difference is not statistically significant.

Patients with poorly differentiated or anaplastic tumours had a significantly lower survival rate than those with well-differentiated tumours or tumours of average grade (*Figure 3*). The probability of surviving 5 years with the latter types of growth was 41 per cent but it was only 11 per cent with anaplastic or poorly-differentiated tumours (log rank $\chi^2 = 17.05$, d.f. = 1, $P < 0.001$).

The probability of survival after 'radical' R_1 resection was also significantly related to the presence of N_1 nodal involvement (*Figure 4*): the 5-year survival of patients with N_1 disease was 18 per cent compared with 60 per cent of patients with N_0 disease (log rank $\chi^2 = 8.67$, d.f. = 1, $P < 0.005$). The survival of the group of 15 patients with N_1 disease might have been improved by the use of the $R_{2/3}$ methods of resection. However, this would have had little effect on the overall survival rate since N_1 patients accounted for only 12 per cent of the total group of 122 patients. Even if all 15 N_1 cases had been cured by a more radical lymphadenectomy (an unlikely assumption since

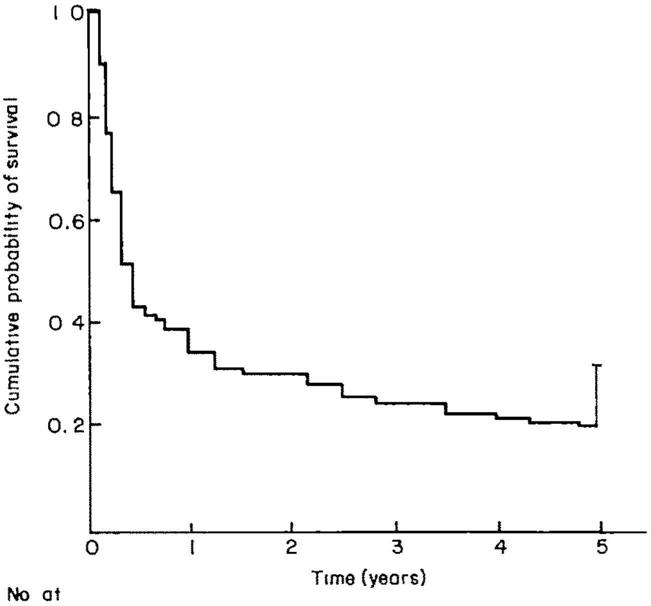

Figure 1 *Age-corrected actuarial 5-year survival of the total group of 122 patients. Error bar represents 95 per cent confidence limit*

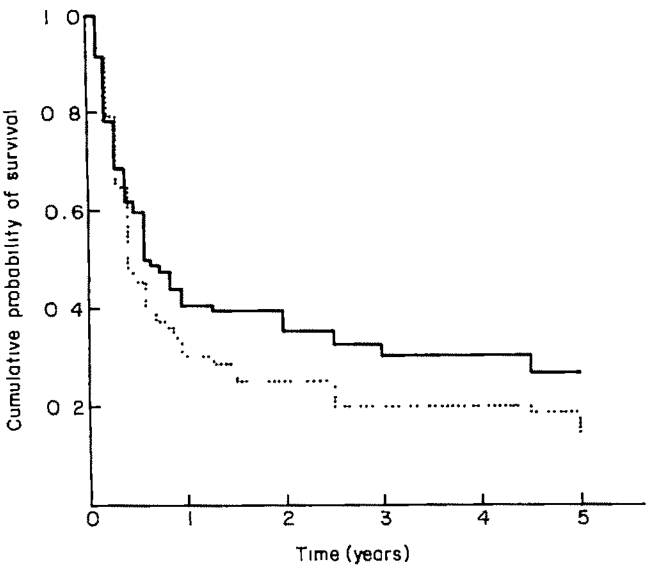

Figure 2 *Age-corrected actuarial 5-year survival for tumours predominantly involving the antrum (——, n=52) and those involving the proximal stomach (······, n=70: 26 M, 28 C, 6 CM, 10 CMA). A, antrum; M, middle or body of stomach; C, cardia*

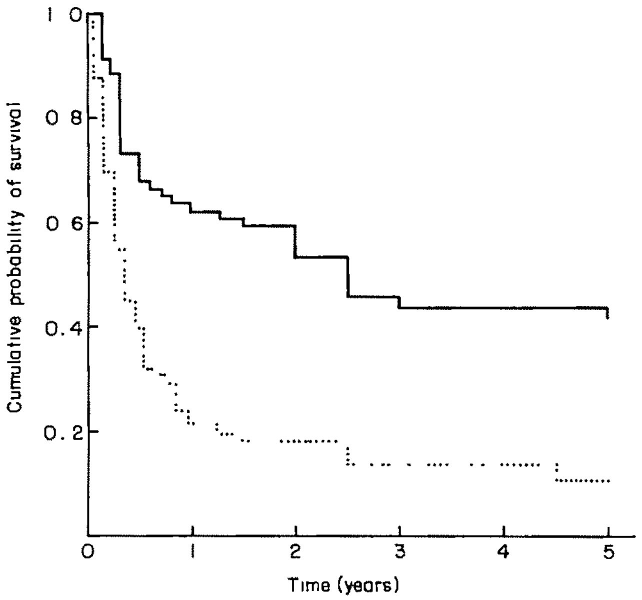

Figure 3 *Age-corrected actuarial 5-year survival for poorly differentiated or anaplastic tumours (······, n=73) and well-differentiated tumours or tumours of average grade (——, n=44). Poorly differentiated or anaplastic growths were associated with a significantly lower survival*

only 60 per cent of N_0 cases were cured by R_1 resection), the 5-year survival rate overall would have increased by only 9 per cent.

Discussion

The 20 per cent 5-year survival for gastric cancer in the present study compares favourably with survival rates of 5–15 per cent described elsewhere in Europe and in the USA[3,13]. The slightly better outcome may be partly due to the low operative mortality following gastric resection in the present study, but it also appears to be related to a rather better prognosis in patients undergoing a potentially curative resection in the absence of lymph node metastases. In a recent study in the USA, Meyers *et al.*[13] found that less than 40 per cent of such cases survived 5 years, whereas the survival rate in the present study was 60 per cent.

Nevertheless, the prognosis of gastric cancer in the UK remains rather poor. The majority of patients in the present study had incurable disease, only 6 per cent had early gastric cancer, and a 'radical' or potentially curative resection by our criteria was possible in only 30 per cent of cases. Using Japanese criteria, an 'absolute curative' resection was possible in only 5 per cent of cases, and this experience contrasts unfavourably with treatment of gastric cancer in Japan. There has been a steady improvement in Japanese survival rates since the 1960s and, probably as a consequence of early detection, a much more favourable type of disease is now encountered[1]. Early gastric cancer confined to the mucosal or submucosal layers of the stomach accounts for 22–56 per cent of cases[1,4], and 'absolute curative' resections are possible in about 40 per cent of patients[5].

It is against this background of a much more favourable type of pathology in Japan that one must assess the claims that extended lymphadenectomy and the more radical $R_{2/3}$ types of gastrectomy have also contributed significantly to the improved survival rates[4,5]. These radical operations are performed with remarkable safety by Japanese surgeons with operative mortality rates of 1–3 per cent, and Kodama *et al.*[4] claimed that the $R_{2/3}$ operations resulted in a 27 per cent improvement in 5-year survival compared with the results of R_1 resection. However, this analysis was not based on the results of a controlled clinical trial and, as Welch[7] has pointed out, such a large increase in survival cannot be explained by a more radical lymphadenectomy alone: only patients with involvement of the $N_{2/3}$ nodes are likely to benefit from the $R_{2/3}$ types of resection; and such metastases are found in only 8–10 per cent of Japanese patients[4,5]. Other important prognostic factors such as the differentiation of the tumour and the depth of invasion through the wall of the stomach are not affected by the methods of gastric resection[14,15] and based on these observations, the maximum gain in survival likely to result from extended lymphadenectomy is around 8–10 per cent assuming that all patients with nodal metastases are cured.

In the present study, the incidence of $N_{2/3}$ metastases in patients undergoing potentially curative resections could not be determined, but 15 patients (12 per cent of the 122 cases) had N_1

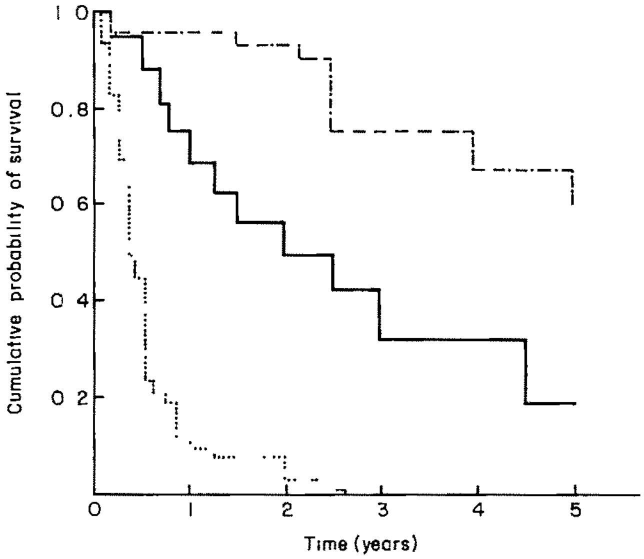

Figure 4 *Age-corrected actuarial 5-year survival following potentially curative or 'radical' resections in patients with no lymph node involvement (N_0) (—·—·—, $P_0H_0N_0S_{0-2}$, n=22) or involvement of the perigastric (N_1) nodes (——, $P_0H_0N_1S_{0-2}$, n=15), and after palliative resections (······, $P_{0-1}H_{0-1}N_{1-4}S_{2-3}$, n=41). P, peritoneal metastases; H, hepatic metastases; N, nodal metastases; S, serosal involvement*

disease and, presumably, some of the patients also had $N_{2/3}$ involvement. Some of these patients might have been cured by $R_{2/3}$ gastric resections, but this would have resulted in a comparatively small improvement in the overall survival rate. Indeed, the 5-year survival rate would have increased by only 9 per cent if all 15 patients had been cured by $R_{2/3}$ gastrectomy. This relatively small benefit in survival must also be weighed against the increased operative risks of extended lymphadenectomy. There was no operative mortality after potentially curative R_1 gastric resections in this study, but some mortality is probable after the more radical methods of gastric resection[3,7,16].

Local or regional recurrence of gastric cancer causes distressing symptoms and palliation is difficult. In the present study 11 per cent of patients undergoing potentially curative gastric resections developed proven locoregional recurrence without evidence of distant metastases. Gastric stump recurrence can be avoided by the use of total gastrectomy rather than partial gastric resections, and it has been suggested that the use of extended lymphadenectomy may reduce the incidence of regional recurrence[2,3].

The results of the present study confirm that the nature of the presenting pathology is the most important determinant of the outcome of treatment for gastric cancer, and it seems probable that further progress in the management of the disease will depend upon earlier diagnosis. The case for more radical methods of gastric resection has yet to be established.

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Randomized comparison of R_1 and R_2 gastrectomy for gastric carcinoma

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The contention that the R_2 radical gastrectomy for localized and potentially curable gastric carcinoma may be superior to gastrectomy without lymphadenectomy (R_1) was assessed by randomized trial. Five years after commencement 403 patients have been evaluated at surgery and only 43 (11 per cent) found eligible (S_{0-2}, P_0, H_0, N_{0-1}), 22 of whom underwent R_1 and 21 R_2 gastrectomy. Seven patients had final histological stages in excess of the protocol. The R_2 group had a longer operating time ($P<0{\cdot}005$), a greater blood transfusion requirement ($P<0{\cdot}005$), a longer hospital stay ($0{\cdot}05>P>0{\cdot}025$) and required reoperation in four cases. There were no postoperative deaths. Four patients have died from the disease in the R_1 group and five in the R_2 group, there being no difference in the probability of survival at a median follow-up of 3·1 years. The small proportion of patients suitable for radical R_2 surgery, the high associated morbidity and the fact that survival advantage has yet to be proven in trial suggest that this procedure should not yet be performed outside of controlled clinical trials.

Keywords: Gastric neoplasms

Survival rates after surgery for gastric carcinoma reported from Japan[1–3] are superior to those in the Western literature. This is partly explained by the early stage of disease encountered there, but none the less stage for stage Japanese patients appear to survive longer[4]. Possible explanations may be that either the tumour has a different biological behaviour or that the radical surgery practised in Japan, which includes extensive lymphadenectomy, is more effective than that performed in the Western world[5]. In this study the R_2 gastrectomy, which includes radical lymphadenectomy, was compared with the R_1 gastrectomy, which does not. The purpose of this evaluation is to identify problems encountered in the course of the trial.

Patients and methods

This trial was approved by the Ethical Research Committee of the Medical Faculty, University of Cape Town. Patients were evaluated, randomized, treated and followed up at Groote Schuur Hospital, Cape Town.

Eligibility

Patients were eligible if at laparotomy the surgeon assessed that the Japanese clinical stage was S_{0-2}, P_0, H_0, N_{0-1}, where: S indicates serosal involvement (none, suspected, definite), P_0 no peritoneal involvement, H_0 no hepatic involvement, and N indicates nodal involvement (none, or group I nodes only)[6]. In terms of the UICC System this meant that the final histological stage would be T_{1-3}, N_{0-1} (with some perigastric N_2 nodes), M_0[7].

Intra-operative histological or cytological confirmation of the stage was not attempted. Patients were excluded if they were older than 75 years, had previous or coexisting malignant disease, had coexisting non-malignant disease which made prolonged follow-up unlikely, or if they came from a remote area.

Randomization and surgical technique

At laparotomy eligible patients were randomly allocated into R_1 or R_2 gastrectomy groups using an ordered set of sealed envelopes containing computer-generated sets of numbers.

A 5 cm proximal and distal gastric clearance in the unstretched stomach was obtained in both types of gastrectomy. Thus, a total gastrectomy was performed for lesions of the proximal third and proximal middle third, the reconstruction being with a 40 cm retrocolic jejunal Roux limb. A subtotal gastrectomy with gastrojejunal anastomosis was performed for lesions of the distal third and some of the distal middle third. The first part of the duodenum was removed with antral tumours. The technique for the R_1 gastrectomy was conservative: the gastrocolic omentum was divided without omentectomy and no formal lymphadenectomy was undertaken other than the removal of the N_1 nodes on the gastric wall. Biopsies for staging were taken from the coeliac, common hepatic and hepatic nodes, and any abnormal nodes. The R_2 gastrectomy was performed as described by Nakajima and Kajitani[8]: the entire greater omentum, superior leaf of the mesocolon, pancreatic capsule and lesser omentum were removed *en bloc* with the stomach. Lymphadenectomy was performed in the infra- and supraduodenal areas and along the hepatic, common hepatic, coeliac and splenic arteries. The left gastric artery was ligated at its origin.

The patients were followed up at 3-month intervals. No attempt was made to screen for recurrence; when, however, patients developed symptoms or signs suggestive of recurrence these were appropriately investigated with endoscopy, ultrasonography and CT scanning.

Analysis

The first patient entered the trial on 2 January 1982 and the last on 11 November 1986. Survival time was assessed 5 years after inception of the trial on 2 January 1987. The χ^2 test with Yates' modification for small numbers and the log rank test were used for statistical comparison.

Results

Over the 5-year period 608 patients were evaluated, 403 came to surgery and 43 (7 per cent overall, 11 per cent at laparotomy) were eligible for the trial. Practically all ineligible patients had advanced disease in excess of the protocol stage.

Twenty-two patients were randomized to have an R_1 gastrectomy and twenty-one an R_2 gastrectomy. The patient characteristics for the two randomized groups were comparable for stage and extent of gastrectomy; by chance the sex ratios were different and the patients in the R_2 group were older (*Table 1*). The pathological assessment showed that seven patients had been understaged at surgery: in the R_1 group two had involved N_2 nodes and two had involved hepatic nodes (N_3); in the R_2 group two patients had involved N_2 nodes and one involved hepatic nodes (N_3). These patients have remained in the trial for analysis.

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Table 1 *Age, sex, stage, protocol violations and operations*

	R_1	R_2
No. of patients	22	21
Age (years) (mean ± s.e.m.)	45·1 ± 8·9	55·8 ± 11·4
Males:females	12:10	15:6
Pathological stage		
T_1	6	7
T_2	5	5
T_3	11	9
N_0	16	14
N_1	2	4
Excess of protocol		
N_2	2	2
N_3	2	1
Total gastrectomy	4	2
Distal gastrectomy	18	19

Table 2 *Morbidity and survival*

	R_1	R_2
Morbidity		
Operating time (h ± s.e.m.)	1·7 ± 0·6	2·33 ± 0·7*
Blood (total units for group)	4	25*
Postoperative stay (days ± s.e.m.)	9·3 ± 4·65	13·9 ± 9·7†
Reoperations	0	4
Pulmonary complications	3	3
Wound infection	0	1
Survival		
Lost to follow-up	1	1
Died from disease	4	5
Alive with recurrent disease	1	0
Alive and well	16	15
Probability of 3-year survival (log rank)	0·78	0·76‡
Protocol violation (patients alive without disease)	1	1

* $P<0{\cdot}005$; † $0{\cdot}05>P>0{\cdot}025$; ‡ $P<0{\cdot}77$

Morbidity and mortality (Table 2)

The patients undergoing the R_2 gastrectomy had a longer operation time ($P<0{\cdot}005$), a greater blood transfusion requirement ($P<0{\cdot}005$) and a longer postoperative hospital stay ($0{\cdot}05>P>0{\cdot}025$). Four patients in the R_2 group required second operations for a retrocolic intestinal herniation after a total gastrectomy, a gastrojejunal leak after subtotal gastrectomy, a right subphrenic abscess and a right hemicolectomy for colon infarction due to late thrombosis of the middle colic artery 4 weeks after surgery. These cases represented first, second, sixth and tenth operations of the R_2 group. Three additional patients in each group suffered respiratory complications. There were no hospital deaths.

Survival (Table 2)

Five years after inception of the trial at a median follow-up of 3·1 years, four patients had died from the disease in the R_1 group and five in the R_2 group (*Table 3*). Four of the seven patients with stages in excess of the protocol have died and a fifth is alive with recurrent disease. Greater numbers and longer follow-up will be required to detect small differences and confer statistical validity on the trial.

Discussion

The aim of the R_2 gastrectomy is excision of the tumour and the draining perigastric nodes, the procedure being curative in the absence of nodal involvement or if only the N_1 nodes are involved[6]. Our criteria for entry ($S_{0-2}, P_0, H_0, N_{0-1}$) identified only 7 per cent of over 608 patients overall or 11 per cent of 403 undergoing surgery as eligible for the trial, the major reason for exclusion being advanced carcinoma. It is clear that most cases in the West present with advanced disease and would not be eligible for a curative R_2 resection[9,10]; this is, however, less often the case in Japan[1–3]. The final histology showed that seven patients had disease stages in excess of the protocol requirement as the stage was underestimated at surgery. When conventional surgery is performed accurate assessment of nodes is not important[11], but intra-operative frozen section or imprint analysis of the N_2 nodes may be necessary when radical surgery is considered. Thus, there are many difficulties not least of which is that any single centre outside Japan is unlikely to have many candidates for the procedure. A multicentre trial—as the British Stomach Cancer Group has in progress—will undoubtedly accrue more patients, but would have the disadvantage of assessment, staging and operations being performed by multiple investigators.

Table 3 *Disease-free survival, actual survival, mode of recurrence and protocol violations**

		Survival (days)		
Case	Stage (operation)	Disease-free	Actual	Recurrence
1	$T_3N_2M_0^*$ (1)	480	503	Ascites, epigastric mass
2	$T_3N_0M_0$ (1)	1230	1276	Ascites, hepatic metastases
3	$T_3N_0M_0$ (1)	296	336	Ascites
4	$T_3N_3M_0^*$ (1)	310	491	Ascites, cervical nodes
5	$T_3N_3M_0^*$ (1)	1780	1780 (alive)	Nil
6	$T_3N_2M_0^*$ (1)	1521	1761 (alive)	Gastric remnant
7	$T_3N_1M_0$ (2)	1140	1263	Wound, abdominal masses
8	$T_2N_1M_0$ (2)	?	150	Hepatic metastases
9	$T_2N_0M_0$ (2)	?	339	Ascites
10	$T_3N_2M_0^*$ (2)	280	320	Gastric remnant
11	$T_3N_2M_0^*$ (2)	690	746	Hepatic metastases
12	$T_3N_3M_0^*$ (2)	630	630 (alive)	Nil

The greater morbidity of the R_2 gastrectomy was significant and cannot be explained by the difference in age of the two groups of patients, the obvious explanation being an inter-relationship of operative complexity and surgical technique. The complications caused a longer hospital stay and four reoperations, all in the first half of the study, while our experience of the procedure was relatively small. The more extensive operation led to a longer operating time and greater blood loss. This higher morbidity and greater cost (as judged by the longer operation times and hospital stays) would have to be outweighed by survival advantage if the procedure were justified.

No such advantage was apparent 5 years after the start of the trial, although a longer follow-up and greater numbers will be necessary to establish any significant difference. It is important to note that the R_2 operation was not compared with the traditional radical gastrectomy (which includes an omentectomy and a partial lymphadenectomy) and over which it might be expected not to show a striking survival advantage. Instead, it was compared with the R_1 gastrectomy where only N_1 nodes are removed.

Most general surgeons will infrequently encounter patients suitable for a R_2 gastrectomy, which is a complex procedure with an appreciable associated morbidity and, as yet, no clear survival advantage proven in trial. The R_2 gastrectomy should not be currently performed outside of controlled clinical trials.

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112

Tightening the loose arterial suture

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In arterial surgery there will inevitably be occasional bleeding from anastomoses. This will sometimes be because of slackness of the arterial sutures. It may result from imperfect technique but can be caused by friable tissues discouraging adequate but necessary tension or by spontaneous loosening as the suture sinks into a bulky and soft intima. When there is slight bleeding from an anastomosis it is usually best to allow time for spontaneous haemostasis to take effect. Further sutures tend to disturb the suture line and lead to renewed bleeding.

When the bleeding is due to a slack continuous suture (*Figure 1a*) there is an easy way to correct the problem. A nerve hook is introduced beneath a loop of the stitch which is drawn out to tighten the line of stitches (*Figure 1b*). The hook is then rotated to twist the loop until it is tight at its base (*Figure 1c*). A silk tie is then placed securely around the base of the loop to maintain this tightness (*Figure 1d* and *e*). A 4/0 Prolene (Ethicon Ltd.) suture tied in this way with 2/0 silk (a monofilament tie would not be appropriate) can support tensions in excess of 100 g. A 2/0 Ethibond (Ethicon Ltd.) suture, which is braided, when similarly tied with 2/0 silk resists tensions exceeding 200 g.

This is a simple technique, and has proved effective on a number of occasions.

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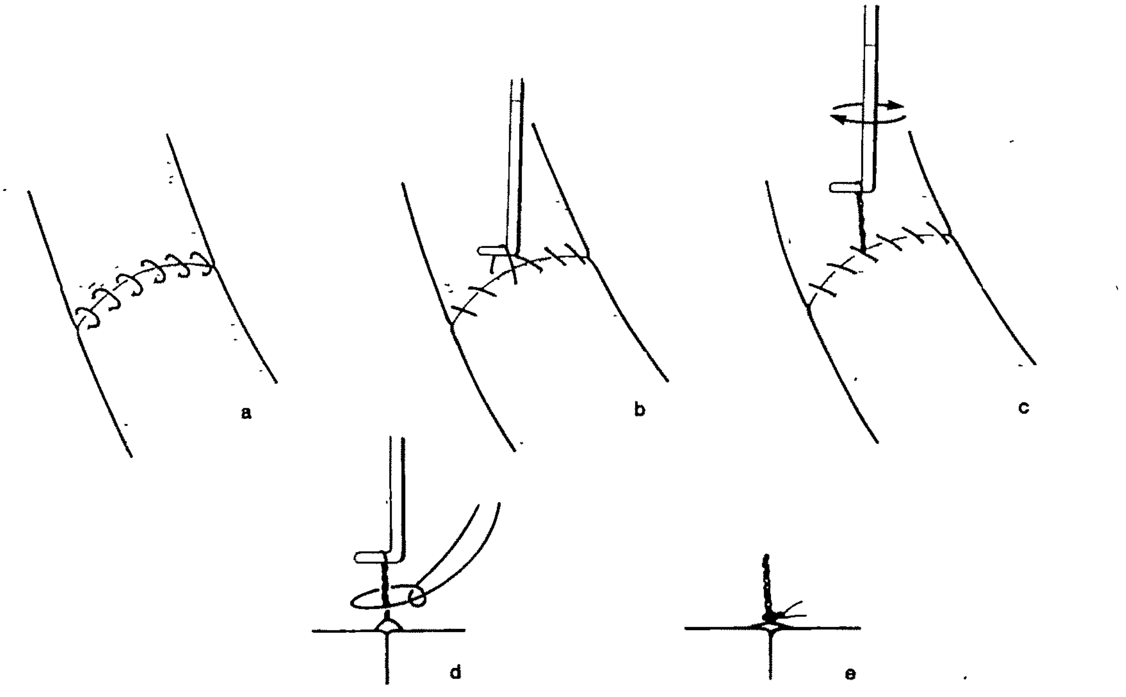

Figure 1 *Tightening the loose arterial suture*

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113–115

Experimental columnar metaplasia in the canine oesophagus

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Regeneration of canine oesophageal mucosa was studied under basal conditions and in the presence of gastro-oesophageal reflux. In normal circumstances mucosal defects in the oesophagus regenerate by squamous epithelium. In the presence of gastro-oesophageal reflux of either acid or a combination of acid and bile, regeneration was frequently by columnar epithelium (Barrett's oesophagus). This columnar regeneration was not seen with bile reflux alone. By the use of squamous barriers to proximal migration of columnar epithelium in the stomach, it was demonstrated that columnar re-epithelialization may occur from cells intrinsic to the oesophagus and is not dependent on proximal migration of cardiac columnar epithelium. The cell of origin of this epithelium may be located in oesophageal gland ducts and is likely to be a multipotential stem cell since the regenerated columnar epithelium may contain goblet and parietal cells not normally found in the oesophagus. This epithelium is morphologically distinct on mucin histochemistry from cardiac columnar epithelium. These findings support the concept that Barrett's epithelium is metaplastic.

Keywords: Oesophagus, regeneration, epithelium, columnar, squamous, Barrett's oesophagus, reflux, metaplasia

The overwhelming weight of evidence supports the view that Barrett's epithelium is an acquired phenomenon secondary to gastro-oesophageal reflux[1–4]. Clinical studies have confirmed severe reflux in patients with Barrett's oseophagus[5,6]. The experimental study of Bremner *et al.*[7] demonstrated that a columnar-lined segment of oesophagus could result from prolonged reflux of acid. Bremner *et al.* suggested that this epithelium was in continuity with cardiac epithelium and had originated from it by proximal migration of cardiac columnar epithelium. Endoscopic studies have shown that the upper limit of columnar epithelium may extend proximally at successive examinations in the presence of continuing reflux[1,2], thereby suggesting that a process of 'creeping substitution' of gastric columnar epithelium may be responsible for the pathogenesis of this condition. However, Barrett's epithelium may include a variety of epithelial types and histological appearances[8], and may present as islands of columnar epithelium remote from the gastric cardia[9]. These findings cannot be explained on the basis of proximal migration of cardiac epithelium alone. Controversy surrounds the pathophysiology of this condition and neither the cell of origin nor the method of replacement of squamous epithelium by columnar epithelium has been established.

The influence of luminal contents on the regenerating oseophageal mucosa is also uncertain and the hypothesis exists that alteration of luminal reflux contents may alter the morphology of the epithelium.

The aim of this study was to establish an animal model of Barrett's oesophagus which would define the pathophysiology of the replacement of squamous epithelium by columnar epithelium. An additional aim was to study the effects of different refluxates on the regenerating oesophageal epithelium.

Materials and methods

Experimental design

Mucosal defects were created in the lower oesophagus of adult mongrel dogs. A 2-cm wide circumferential ring of squamous mucosa was removed from the lower end of the oesophagus. The excised mucosa extended distally to the squamocolumnar junction for one-half of the circumference of the cardia. A thin strip of squamous epithelium was retained in the other half so that the squamocolumnar junction could be precisely defined at histological examination. A 2-cm wide normal ring of squamous mucosa was left intact above this defect and a further 2-cm wide ring of squamous mucosa circumferentially excised above this (*Figure 1*). In one group of dogs (group 4) two circumferential rings of squamous mucosa were excised leaving an intact 2-cm wide ring between these in the region of the mid-oesophagus and did not involve the gastro-oesophageal junction.

Twenty-five adult mongrel dogs were studied for 3 months and were separated into five groups.

Group 1 (n=6). This group had a Wendel cardioplasty[7] and fixed hiatus hernia performed through a left thoracotomy. Mucosal defects were created as illustrated in *Figure 1*. Postoperatively this group was given 100 μg pentagastrin subcutaneously daily to augment acid reflux and was designated an 'acid' group.

Group 2 (n=6). These animals had a cardioplasty, hiatus hernia and mucosal defects as in *Figure 1*. In addition, a biliary diversion was performed by ligating the common bile duct and establishing a cholecystogastrostomy high on the lesser curve of the stomach. This group was designated an 'acid + bile' group. No pentagastrin was given.

Group 3 (n=6). This group had the same operative procedure as

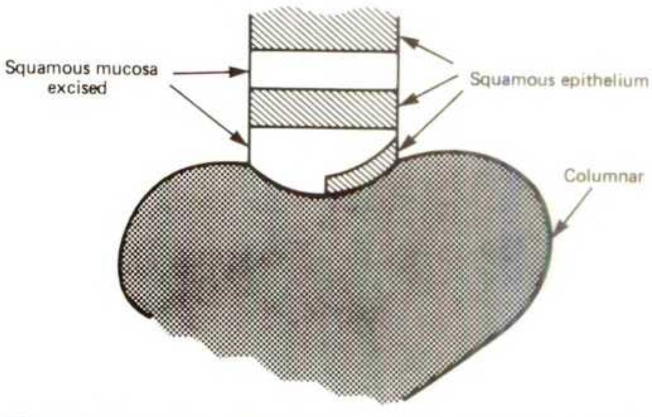

Figure 1 *The experimental design created 'upper' and 'lower' ring mucosal defects in the oesophagus with intervening normal squamous epithelial barrier. Half of the squamocolumnar junction has been left in* situ *and half excised*

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Table 1 *Pre- and postoperative lower oesophageal sphincter pressures (LOSP) in groups 1–4*

Group	Pre-operative LOSP (mmHg)	Postoperative LOSP (mmHg)	Significance
1	13·5±5·5	3·7±1·5	$P<0{\cdot}01$
2	22·1±2·7	6·5±1·3	$P<0{\cdot}001$
3	13·0±2·2	4·6±1·2	$P<0{\cdot}01$
4	20·0±5·0	15·0±2·9	n.s.

Figures are mean ± s.d. Analysed using the Student's *t* test

Table 2 *Pre- and postoperative intragastric bile acid concentrations*

Group	Pre-operative (μm/l)	Postoperative (μm/l)	Significance
1	0·3±0·2	0·4±0·2	n.s.
2	0·1±0·005	4·6±1·4*	$P<0{\cdot}0001$
3	0·8±0·004	4·2±1·2*	$P<0{\cdot}0001$

Figures in mmol/l (mean ± s.e.m.). Analysed using the Wilcoxon rank sum test

Table 3 *Histology results in operative groups*

Group	Positive (columnar re-epithelialization)	Negative (squamous regeneration)
1	5 (2 in both rings)	1
2	3	3
3	0	6
4	0	3

group 2 dogs but received cimetidine 800 mg twice daily postoperatively.

Group 4 (n = *3*). Through a longitudinal oesophagotomy in the mid-oesophagus mucosal defects were created by excising two circumferential rings of squamous mucosa and leaving a 2-cm wide ring intact. The oesophagus was resutured longitudinally, thereby maintaining normal function in the lower oseophageal sphincter.

Group 5 (n = *4*). This group was used as a histological control. Multiple longitudinal sections from lower oesophagus to upper stomach across the gastro-oesophageal junction were taken to establish normal histology of this region.

Histology

When the animals were killed, the oesophagogastrectomy specimens were excised *en bloc* and inflated with and then fixed in formalin. After fixation the specimens were opened along their anterior borders and pinned out. Multiple longitudinal sections 2 mm wide were taken from the posterior wall of the lower oesophagus to upper stomach across the gastro-oesophageal junction. These sections were taken in identical fashion to control sections. The 2-mm wide sections were rolled up and sections 5 μm thick were taken in a longitudinal fashion to ensure histological continuity in one section from lower oesophagus to upper stomach across the gastro-oesophageal junction. Sections were considered 'positive' if columnar re-epithelialization had occurred in areas previously lined by squamous epithelium in either the 'lower' or 'upper' ring areas. Sections were considered 'negative' if re-epithelialization was by squamous epithelium and neither ring showed evidence of columnar re-epithelialization.

Statistical analysis

This was either Student's *t* test or Wilcoxon rank sum test as appropriate.

Pre- and postoperative studies

Manometry. All dogs had manometric estimation of the lower oesophageal sphincter pressure using a station pull-through technique[11]. This was performed pre-operatively and at 6 and 12 weeks postoperatively.

Intra-oesophageal pH recording. All animals had intra-oesophageal pH studied by placement of a pH probe (Synectics) 5 cm above the manometrically identified sphincter. The studies were performed for a 4-h period in the awake unanaesthetized animal. The pH recordings were performed pre-operatively and at 6 and 12 weeks postoperatively.

Intragastric bile acid concentrations. Intragastric bile acid concentrations were assayed by an enzymatic technique[10] on samples of aspirated gastric juice. This was performed pre-operatively and at 6 and 12 weeks postoperatively.

Results

Pre- and postoperative studies

Lower oesophageal sphincter pressure (*LOSP*). A significant reduction in LOSP was demonstrated in all animal groups after the cardioplasty procedure (*Table 1*). No significant difference in LOSP was demonstrated in group 4 pre- and postoperatively.

Intra-oesophageal pH recordings. Only one spontaneous reflux event was documented pre-operatively in one dog. This was cleared rapidly. Gross reflux was always seen after the

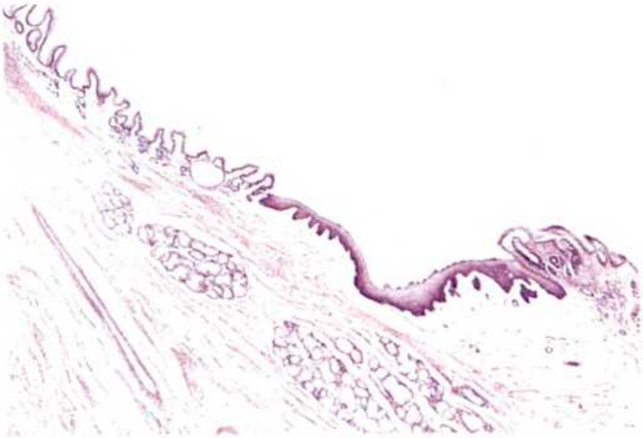

Figure 2 *Experimentally induced columnar epitherlium is demonstrated (on the left) above the squamous barrier in the oesophagus overlying deep oesophageal glands. Columnar epithelium (on the right) below the squamous barrier is also seen*

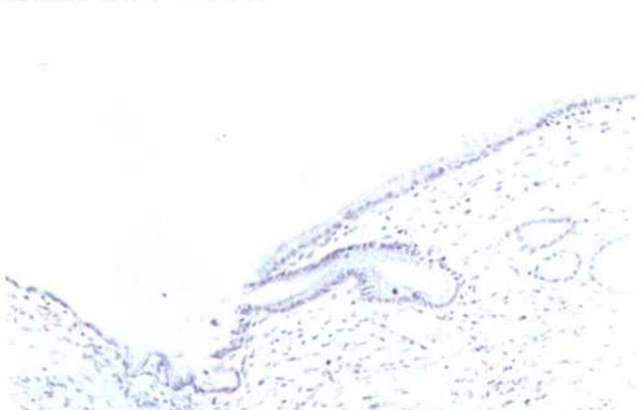

Figure 3 *Section illustrating an oesophageal gland duct lined by cuboidal type epithelium in continuity with surface ulceration and beginning to re-epithelialize this area with columnar epithelium*

cardioplasty procedure except in the cimetidine group (group 3). No reflux events were recorded in group 4 where the sphincteric mechanism had been left intact.

Intragastric bile acid concentrations. *Table 2* illustrates the range of intragastric bile acid concentrations pre- and postoperatively in the animal groups.

Histology

Table 3 illustrates the histology results. Group 1 ('acid' group) demonstrated columnar re-epithelialization in the lower ring in five dogs (*Figure 2*). Two dogs in this group also had columnar re-epithelialization in the upper ring above the intact squamous barrier. In group 2 ('acid + bile') three dogs demonstrated columnar re-epithelialization in the lower ring and three dogs underwent squamous re-epithelialization. No animal in group 3 (cimetidine) demonstrated columnar re-epithelialization of the mucosal defects and squamous re-epithelialization was seen in all cases. In the absence of reflux, mucosal defects healed by squamous epithelium in all animals in group 4.

In areas which still demonstrated some ulceration, oesophageal gland ducts were seen in continuity with luminal contents and re-epithelialization was evident extending from the necks of these glands to adjacent ulcerated areas (*Figure 3*).

Morphology

The regenerated columnar epithelium was villiform in pattern and occasionally demonstrated both goblet and parietal cells but the pseudo-absorptive cells seen in specialized intestinal-type Barrett's epithelium in man was not seen. Periodic acid-Schiff and Alcian Blue staining demonstrated morphological differences in the mucin distribution in the experimental Barrett's epithelium and cardiac mucosa. Neutral mucin was present throughout the supranuclear region in experimental columnar epithelium, in contrast to the gastric epithelium where its distribution was in the apical portion of the cell.

Discussion

In these studies we have demonstrated that oesophageal mucosal regeneration in the absence of reflux occurs by squamous epithelium, a finding previously reported by other workers[12,13]. Columnar re-epithelialization of oesophageal mucosal defects may occur under conditions of augmented acid reflux as previously reported by Bremner *et al.*[7]. Columnar re-epithelialization may also occur when a combination of acid and bile reflux is present. This has not been reported previously. The administration of cimetidine to the unstimulated 'acid + bile' group to produce a model of bile reflux alone prevented columnar re-epithelialization. This suggests that bile reflux alone may be insufficient to produce a columnar-lined segment. This finding appears contrary to published reports of Barrett's epithelium developing some years after total gastrectomy[14] where acid reflux is no longer possible. However, such patients are likely to have had a refluxate containing bile, duodenal and possibly pancreatic juice as well—a refluxate not studied in this experimental model.

This study has demonstrated by the use of squamous barriers to proximal migration of gastric columnar epithelium that columnar epithelium may develop in the oesophagus proper from cells intrinsic to that region. Columnar re-epithelialization of the upper ring could not have resulted from proximal migration or by a process of 'creeping substitution' of gastric columnar epithelium. This experimental study introduces new concepts about the pathogenesis of Barrett's epithelium.

The demonstration of regenerating columnar epithelium originating from cells lining oesophageal gland ducts suggests that this is the cell of origin of this epithelium. Oesophageal gland ducts in both the dog and man may possess a squamo-cuboidal junction at varying levels within the duct lining. Reflux-induced mucosal injury may then expose cuboidal cells and possibly stem cells to luminal reflux. It has been postulated[8] that stem cells in the oesophagus possess multipotentiality for cell differentiation and that this would account for the variety of cell types and histological appearances seen in Barrett's epithelium in man. This variety of histological appearances is unlikely to be accounted for by proximal migration of cardiac epithelium alone.

The demonstration of goblet and parietal cells and a morphologically distinct epithelium from cardiac epithelium has not been previously described and supports the metaplastic nature of Barrett's epithelium in man.

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A rational technique for surgical operation on Borrmann type 4 gastric carcinoma: left upper abdominal evisceration plus Appleby's method

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Borrmann type 4 gastric carcinoma, including linitis plastica, *is difficult to detect at an early stage and the results of surgical treatment remain poor. We have used 'left upper abdominal evisceration plus Appleby's method (LUAE + Apl.)' as a radical surgical procedure for this disease. During the period 1983–86, 30 cases of Borrmann type 4 gastric carcinoma underwent this procedure (Group A). These cases were compared with 30 patients who underwent total gastrectomy with pancreaticosplenectomy (Group B) during the period 1980–82. Although this is not a randomized study and the extent of resection was greater in Group A, the operation time, amount of blood loss, and number of complications were similar for both methods. When the survival rates were compared, the 3-year survival rate in stage II–III cases was higher for Group A (83·3 per cent) than for Group B (42·2 per cent)* ($P < 0{\cdot}05$). *One patient in Group A and 12 patients in Group B died with peritoneal metastasis within 3 years of operation in stage II–III. The LUAE + Apl. method is a rational and useful technique for the surgical treatment of Borrmann type 4 gastric carcinoma.*

Keywords: Gastric cancer, Borrmann type 4, left upper abdominal evisceration, Appleby's method

Gastric cancers that are flat without any craters and wide-spreading macroscopically, are usually discovered at a very advanced stage[1]. Various attempts have been made to detect these so-called Borrmann type 4 carcinomas (including *linitis plastica*) at an earlier stage, but no method for this has yet been generally accepted[2,3]. The results of surgical treatment of Borrmann type 4 gastric carcinoma remain very poor, and the 5-year survival rate even in curable resection cases has ranged from 10 to 20 per cent[4] during the past 20 years. In recurrent cases, ascites is occasionally observed, and the relapsed lesion shows a peritoneal growth pattern with luminal stenosis and formation of conglomerates in the lumen in most cases[3,5]. It is thought that these relapses are not attributable to intra-abdominal dissemination of cancer cells but to residual cancer cells which have infiltrated around the primary lesion to invade the lower abdominal area along the posterior peritoneum and gut[6,7]. We have employed left upper abdominal evisceration plus Appleby's method[8] (LUAE + Apl.) with the aim of not leaving any remnant of cancer in the vicinity of the primary lesion. With this operative technique, the stomach and surrounding viscera (transverse colon, pancreas body and tail, spleen and left adrenal gland) are resected *en bloc*. When surgery is performed by this method, the lymph nodes of the left upper abdomen can be dissected easily at the same time. We have employed this method for surgery on patients with Borrmann type 4 carcinomas for the last 4 years. In the study described here, we evaluate this method in comparison with other operative techniques which were used before this series.

Patients and methods

Borrmann type 4 gastric cancers including *linitis plastica* are defined as advanced cancers which are flat without any craters and wide-spreading (more than 8 cm in diameter) macroscopically. To treat such cancers, the LUAE + Apl. method is a rational and adequate operative technique which combines removal of the stomach and surrounding viscera, and complete dissection of distant lymph nodes (n_2), as described by Appleby[8].

In 30 cases of Borrmann type 4 gastric carcinoma which were operated on in our department during the period 1983–86, we employed the LUAE + Apl. method (Group A). The control group (Group B) consisted of 30 patients with Borrmann type 4 gastric carcinoma who underwent total gastrectomy with pancreaticosplenectomy during the period 1980–82. The patients of Group A and Group B were consecutive and this is not a randomized study. In each period, each operation method was performed, whenever possible, on patients younger than 70 years of age and without any liver metastasis, peritoneal metastasis in the lower abdomen or severe complications. The numbers of patients in stage II–III (less advanced cases)[9] and stage IV (highly advanced cases) were 11 and 19 respectively in Group A and 19 and 11 in Group B. The remaining patients during both study periods underwent palliative gastrectomy, gastroenterostomy or laparotomy only.

In the LUAE + Apl. method, total gastrectomy was performed together with resection of the transverse colon, pancreas body and tail, spleen, and left adrenal gland *en bloc*. Compared with total gastrectomy with pancreaticosplenectomy, this method is advantageous in that the mesocolon of the transverse colon and tissues of the dorsal area of the pancreas body and tail are resected at the same time. Moreover, lymph node dissection can be easily performed in the proximal portion of the coeliac axis, hepatoduodenal ligament and para-aortic nodes (*Figure 1*). Operative reconstruction was achieved by Roux-en-Y oesophago-jejunostomy and colocolic anastomosis.

Adjuvant treatment was prescribed in all cases. Three regimens were used chronologically, consisting of Type a: Mitomycin C (10 mg × 3) + 5fluorouracil (150 mg/day for 1 year); Type b: Mitomycin C + tegafur (1-(2-tetrahydrofuryl)-5-fluorouracil) (600 mg/day for 1 year); and Type c: Mitomycin C + uracil plus futraful preparation (combination: 1-(2-tetrahydrofuryl)-5-fluorouracil and 2,4(1H,3H-pyrimidinedione) (400 mg/day for 1 year). Type a, b and c treatments were used in 3 cases, 15 cases and 12 cases in Group A, respectively, and in 18, 9 and 3 cases, respectively, in Group B.

Table 1 shows the sex and age of the patients, depth of invasion of the

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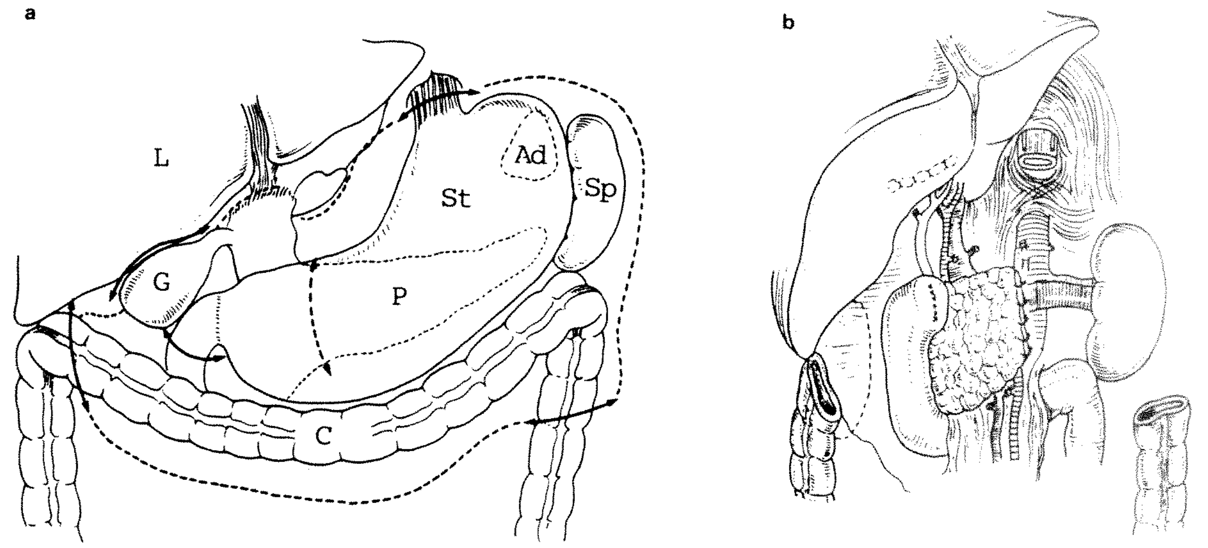

Figure 1 *Diagrammatic representation of left upper abdominal evisceration (LUAE) + Appleby's method (Apl.).* **a**, *Organs to be removed;* **b**, *left upper abdomen after LUAE + Apl. L, liver; G, gallbladder; St, stomach; P, pancreas; Ad, left adrenal gland; Sp, spleen; C, transverse colon*

Table 1 *Demographic and clinicopathological variables in patients subjected to left upper abdominal evisceration + Appleby's method (Group A) and total gastrectomy with pancreaticosplenectomy (Group B)*

	No. of patients	
	Group A	Group B
Age (years)		
30–59	19	17
60–69	11	13
Sex		
Male	12	19
Female	18	11
Invasion of gastric wall		
Not deeper than subserosal layer (-ss)	8	7
Exposed to serosa (se, si)	22	23
Nodal status		
Positive		
Regional nodes (n_1)*	5	6
Distant nodes (n_2, n_3, n_4)†	17	18
Negative	8	6

*n_1, Right cardiac, left cardiac, lesser curvature, greater curvature, suprapyloric and infrapyloric lymph nodes

†n_2, Left gastric artery, common hepatic artery, coeliac axis, splenic hilar and splenic artery lymph nodes

n_3, Hepatoduodenal ligament, posterior aspect of pançreas and root of mesentery lymph nodes

n_4, Mesocolonic and para-aortic lymph nodes

gastric wall and nodal status. With respect to the distribution of cases by age, no difference was seen between Group A and Group B. The incidence of female patients was higher in Group A, although the difference was not statistically significant. With regard to the depth on invasion of the gastric wall, spread had occurred to the serosa in most of the cases. As to nodal metastasis, no significant difference was seen between Group A and Group B in either the positivity rate or the incidence of distant nodal metastasis.

Comparisons were made between these groups in terms of the operation time, the amount of blood loss, the number of postoperative complications (pancreatic fistula and liver dysfunction) and the survival rate.

Kaplan–Meier's method was used to prepare the survival curve. For statistical analysis, the log rank test and the Z test (χ^2 test) was used.

Table 2 *Operation time, blood loss and the incidence of postoperative pancreatic and hepatic disorders*

	No. of patients	
	Group A	Group B
Operation time (h)		
≤4	0	8
4·1–6	20	12
≥6·1	10	10
Blood loss (ml)		
≤1000	8	9
1001–2000	19	16
≥2001	3	5
(median)	(1200)	(1500)
Pancreatic fistula		
Positive	7	9
Negative	23	21
Hepatic disorder		
Positive		
Mild	11	14
Severe	3	3
Negative	16	13

Results

As shown in *Table 2*, the operation was completed within 6 h in most of the cases in Group A, but took less than 4 h in some Group B patients. The amount of blood loss was < 1000 ml in some cases in both Group A and B but in most cases it was 1001–2000 ml, with little or no difference between the groups. The median volume of blood loss was 1200 ml in Group A and 1500 ml in Group B. With regard to postoperative complications, liver dysfunction was observed as an elevation in serum glutamic oxaloacetic transaminase (100–250 units/l) and/or serum glutamic pyruvic transaminase (100–200 units/litre) immediately after LUAE + Apl., although these values returned to normal in about 1 week and there was no difference between Group A and Group B in the degree of liver disturbance at the fourth postoperative week. The incidence of postoperative pancreatitis and pancreatic fistula, which occur frequently after pancreatectomy, was not different when Group A (23 per cent) and Group B (30 per cent) were compared. We experienced no leaks from colonic anastomoses. The postoperative follow-up period for the patients in Group A was 18·6 ± 12·9 months and

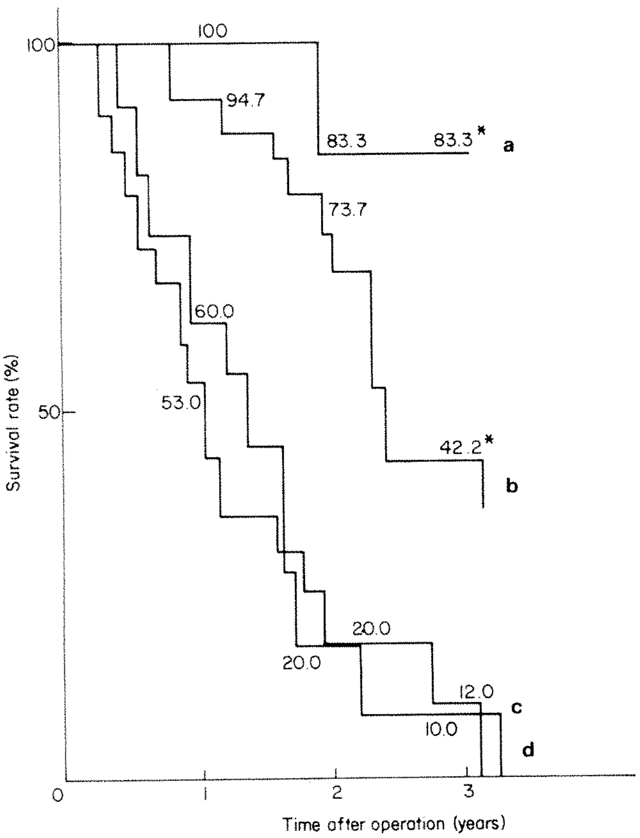

Figure 2 *Survival curve of Borrmann type 4 gastric carcinoma in Groups A and B.* **a**, *11 patients received LUAE + Apl. operation (Group A) in stage II–III;* **b**, *19 patients in stage II–III received total gastrectomy combined with pancreaticosplenic resection (Group B);* **c**, *19 patients in stage IV received LUAE + Apl. operation (Group A);* **d**, *11 patients in stage IV received total gastrectomy combined with pancreaticosplenic resection (Group B);* $^*P<0\cdot05$ **a** *versus* **b**

that in Group B was 28·4 ± 19·0 months. There were no deaths within 30 days of operation in either group (see Discussion). In highly advanced cases (stage IV)[9], no difference in survival rate was found between the two groups, while the 3-year survival rate in less advanced cases (stages II–III) was higher in Group A (83·3 per cent) than Group B (42·2 per cent, $P<0\cdot05$; *Figure 2*). The 3-year survival rate of the patients who received Type a adjuvant treatment was 40 per cent in stage II–III and 12 per cent in stage IV; the rates with Type b therapy were 55 and 10 per cent and with Type c 66 and 20 per cent, respectively. There was no significant difference between the survival rates with Type a and Type b, between Type b and Type c, or between Type a and Type c. The mode of recurrence in most of the deaths in both groups was in the form of peritoneal metastasis, which could be divided into 'ascites type' and 'retroperitoneum-invading type' (causing luminal stenosis with or without ascites). In Group A the causes of death were ascites-type peritoneal metastasis (12), retroperitoneum-invading metastasis (4) and liver dysfunction (1). In Group B, they were ascites-type peritoneal metastasis (5), retroperitoneum-invading metastasis (19) and other diseases (3).

Discussion

Early detection of Borrmann type 4 gastric carcinoma is difficult and in our series of patients none were classified as stage I, while stage II cases accounted for only 6·7 per cent (four cases) of the total.

Appleby's method is used in operations on advanced carcinomas. With this method, the coeliac axis and the common hepatic artery are dissected together with lymph nodes, and it has been reported to be a very safe method[8]. However, we encountered one problem associated with Appleby's method: one patient in the present series died within 99 days of operation after developing liver necrosis due to an abnormality of the hepatic artery. In view of this experience, we perform angiography before conducting operations by Appleby's method. In our 25 most recent cases, the hepatic artery showed a normal course from the coeliac axis giving rise to the common hepatic artery which then divided into right and left hepatic artery in 60 per cent of cases, the remaining cases showing some abnormality in the hepatic artery system. We abandoned Appleby's method in 16 per cent of cases because there was a possibility that the blood supply to the liver might be compromised. By taking these precautions, we have experienced no problems with operations by Appleby's method in recent years but wish to stress that angiography must be performed without fail before operation.

LUAE is an operative technique by which the stomach and its surrounding viscera are resected *en bloc* together with the serosa in order to leave no remnant of cancer. Although many visceral organs, including the transverse colon (and sometimes the right half of the colon), pancreas body and tail and left adrenal gland are resected simultaneously in this method, no great difference was seen in the incidence of postoperative complications compared with the method of total gastrectomy combined with pancreaticosplenic resection. We believe that there may be an indication for this method in cases of progressive carcinomas other than Borrmann type 4 carcinoma when there is a strong tendency for infiltration of the surrounding visceral organs.

Because the incidence of nodal metastasis is high in cases of Borrmann type 4 gastric carcinoma, lymph node dissection also constitutes an important part of the operative procedure in these cases. When the operation is done by the LUAE + Apl. method, the coeliac axis as well as distant nodes (including the hepatohilar and para-aortic nodes) can easily be resected *en bloc* simultaneously with resection of the surrounding viscera. On the other hand, in the method of total gastrectomy with combined pancreaticosplenic resection, it is impossible to perform *en bloc* dissection of distant nodes[10,11].

Comparison of the survival curves following the two types of surgical operation reveals little difference between Groups A and B in stage IV (highly advanced cases). In highly advanced cases, small cell nests may remain in the lower abdomen even after LUAE + Apl. operation. In less advanced cases (stage II–III) there is a statistically significant difference in the 3-year survival rate between the two groups in that the LUAE + Apl. method was more effective in the treatment of Borrmann type 4 gastric carcinoma. One patient in Group A and twelve patients in Group B died with peritoneal metastasis within 3 years of operation in stage II–III. On the basis of these findings, in our opinion, the LUAE + Apl. method is a rational operative method for use in the treatment of Borrmann type 4 gastric carcinomas.

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Case report

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Isolated pyloric obstruction in association with large hiatus herniae

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Obstruction of the stomach in association with a hiatus hernia is an unusual condition[1,2]. Obstruction of the stomach is most common in para-oesophageal herniae and the rare herniae of the foramen of Morgagni, but also arises in sliding hiatus herniae when gastric rotation leads to a volvulus[3,4]. Two main patterns of volvulus in hiatus herniae have been reported. In one type rotation around the long axis of the stomach occurs, most commonly in large para-oesophageal herniae. In the other, partial or complete rotation occurs around the axis of the gastric mesenteries leading to inlet and outlet blockage[2,5].

Obstruction of the pylorus by entrapment in a hiatus hernia without gastric rotation does not appear to have been reported. We describe three cases of entrapment of a mobile first part of the duodenum between the stomach and crura in large hiatus herniae, causing gastric outlet obstruction without the presence of a volvulus.

Case reports

Case 1

An 82-year-old woman presented with vomiting of 24 h duration causing dehydration and hypotension. The metabolic disturbance was corrected with intravenous fluids and a barium meal examination was performed (*Figure 1*). There was free flow of contrast into the stomach, which appeared normal apart from the presence of a large sliding hiatus hernia. There was no passage of contrast beyond the pylorus which lay unusually high in the abdomen. At operation the first part of the duodenum was found to be caught between the right diaphragmatic crus and the intrathoracic stomach. There was no gastric rotation. Duodenum and stomach were reduced without difficulty and were undamaged. A crural repair and anterior gastropexy was performed and the patient made an uneventful recovery. There was no recurrence or further trouble 1 year later.

Case 2

A 78-year-old woman presented with one day's copious vomiting and mild epigastric discomfort. For the previous 6 months she had had occasional episodes of water brash and vomiting, but no previous history of indigestion or dyspepsia. Two months earlier she had been admitted with a similar episode of vomiting. A diagnosis of hiatus hernia had been made but endoscopy failed because of profuse vomiting. Her symptoms had settled and she had been allowed home. On readmission she was dehydrated but abdominal examination was normal. A chest X-ray showed a large hiatus hernia. Vomiting persisted and a barium meal examination was performed which showed a normally orientated stomach lying mainly in the chest with the antrum within the abdomen (*Figure 2*). The pylorus was drawn up into the hiatus and complete gastric obstruction had occurred. At operation these findings were confirmed and a small duodenal ulcer palpated. The obstructed pylorus was easily reduced and the stomach brought down into the abdomen. A Nissen repair was performed and a gastropexy fashioned between anterior stomach and the abdominal wall. Her subsequent recovery was uneventful, and the symptoms have not recurred.

Case 3

A 78-year-old woman presented with a 2 day history of coffee ground vomiting. She had previously complained of occasional heartburn and epigastric discomfort. A succussion splash could be demonstrated in the abdomen. Following resuscitation an emergency endoscopy was performed which showed distal oesophagitis and an enlarged stomach of normal orientation with gastric outlet obstruction. A barium meal

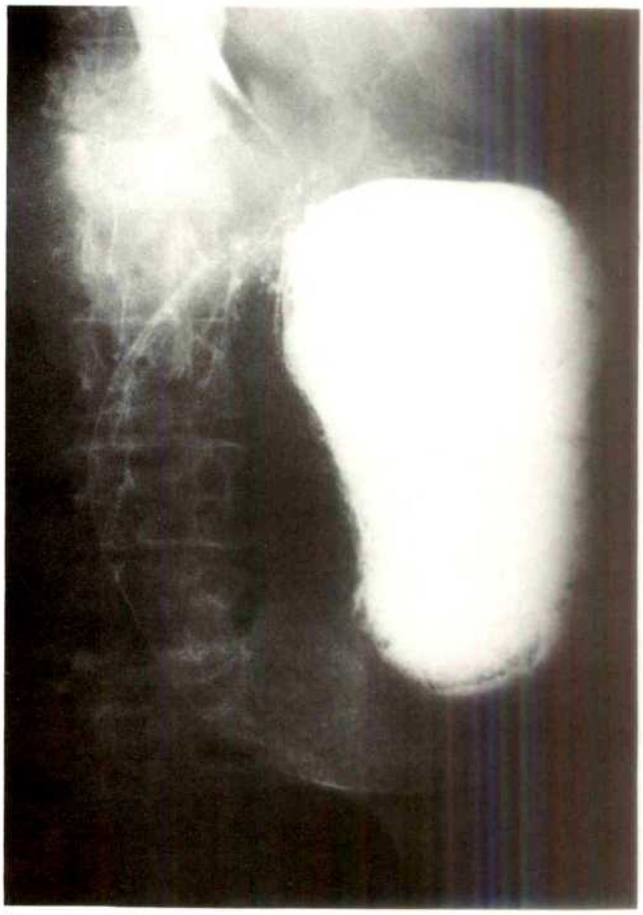

Figure 1 *Barium meal examination showing entrapment of intrathoracic pylorus*

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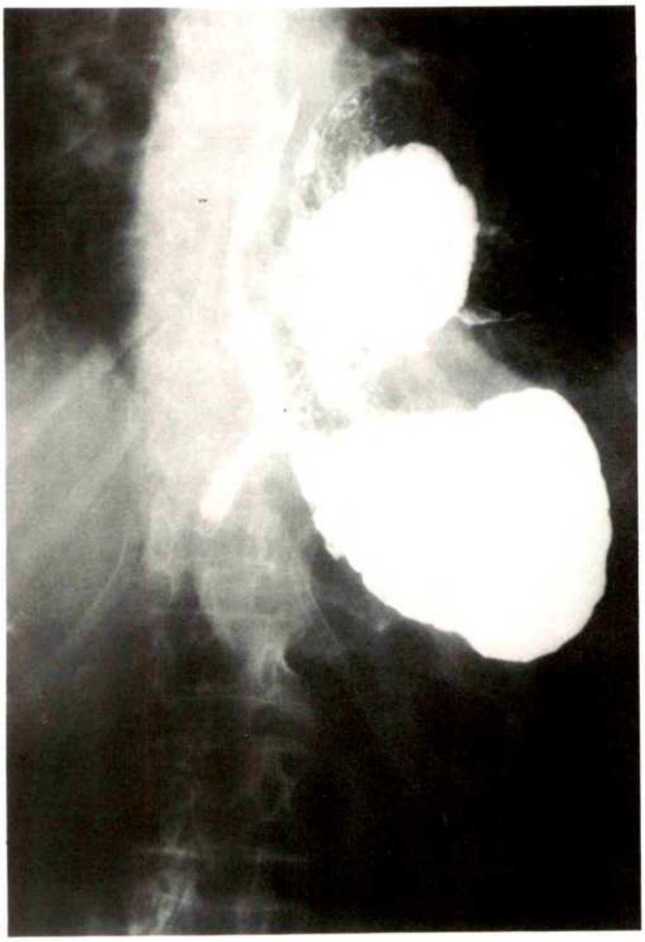

Figure 2 *Barium meal examination showing intra-abdominal antrum with pyloric obstruction at the crura*

examination confirmed a rolling hiatus hernia obstructed at the pylorus. Emergency surgery was performed and the pylorus was found trapped between the diaphragmatic hiatus and the fundus of the stomach. The obstruction was reduced and the stomach brought into the abdomen. There was no other gastric rotation. An anterior crural repair, Nissen fundoplication and anterior gastropexy were carried out. The patient made a normal postoperative recovery.

Discussion

Although many forms of intestinal obstruction have been described in relation to hiatus herniae, we have been unable to discover previous reports of cases in which pyloric obstruction occurred in the presence of a normally orientated stomach. Entrapment of the antrum is well recognized in para-oesophageal herniae where the cardia remains below the diaphragm[3]. Organo-axial volvulus, rotation round the long axis of the stomach, and mesenterio-axial volvulus around the gastric mesenteries are equally well known in both acute and chronic forms, either as complete twists with obstruction of the blood supply leading to emergency presentation, or as intermittent rotations producing long-standing symptoms[1,2]. The commonest form of obstruction is in a para-oesophageal hernia, presumably because gastric rotation is greatest when the cardia remains in the abdomen.

In our cases the relation of cardia, fundus and antrum was preserved despite variable degrees of displacement into the chest. All the patients were elderly and malnourished. The first and second parts of the duodenum had become unusually mobile and had been brought nearer to the diaphragm by upward migration of the stomach. It is possible that during an episode of raised intra-abdominal pressure the pylorus was displaced upwards into the chest and held between the crura and body of stomach, leading to complete gastric obstruction and acute presentation. The appearances of the duodenum at operation in these cases did not suggest chronic displacement. The presence of a duodenal ulcer in one patient may have been coincidental in view of the high incidence of ulcer disease in association with hiatus hernia[6], but might also represent a consequence of stasis and vascular occlusion.

The distinction of this condition from obstruction due to a volvulus has some practical value. Acute volvulus is associated with a high incidence of infarction and urgent surgery may be required even before resuscitation is completed. In contrast isolated pyloric obstruction is less likely to cause strangulation and measured resuscitation may be used with potential benefit to often elderly patients. We consider the use of emergency gastric radiology to be an important early step in the management of patients with high intestinal obstruction.

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Anterior lesser curve seromyotomy with posterior truncal vagotomy versus proximal gastric vagotomy

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In a prospective randomized trial anterior lesser curve seromyotomy with posterior truncal vagotomy (ASPTV, $n=48$*) has been compared with proximal gastric vagotomy (PGV,* $n=43$*). Eighty-eight and eighty-three patients were available for follow-up studies at 1 year and 2 years, respectively. Six months postoperatively the mean reduction in pentagastrin-stimulated peak acid output (PAO) was 48·5 per cent (s.d. 26·3) after PGV and 50·5 per cent (s.d. 23·3) after ASPTV. Two years after the operation satisfactory clinical results (Visick I + II) were found in 84·2 per cent of the patients after PGV and in 88·9 per cent after ASPTV. There was a significant difference in the duration of surgery. No serious postoperative gastric sequelae were encountered after either operation. Up till January 1987, eight endoscopically proven, symptomatic recurrent ulcers have been diagnosed: four in the PGV group (9·3 per cent) and four in the ASPTV group (8·7 per cent). The results of this randomized study suggest that ASPTV is as good as PGV in the surgical treatment of chronic duodenal ulcers.*

Keywords: Chronic duodenal ulcer, proximal gastric vagotomy, highly selective vagotomy, anterior seromyotomy and posterior truncal vagotomy, recurrent ulcer

Although proximal gastric vagotomy (PGV) had been shown to be effective in the surgical treatment of chronic duodenal ulcers, and although it combines a very low surgical mortality rate[1] with few if any postoperative gastric sequelae[2], its firm place in the armamentarium of treatments for duodenal ulcers has yet to be established. The disadvantages of PGV, besides the small risk of ischaemic necrosis of the lesser curvature and damage to the nerves of Latarjet, are that the operation is time-consuming and is often technically difficult to perform. These factors could lead to inadequate denervation of the parietal cell mass and might explain some of the less impressive results reported in the literature[3–6] compared with those produced by the highly experienced pioneers of the procedure[7,8]. Taylor tried to overcome these problems by a lesser curve superficial seromyotomy on both sides of the stomach[9]. Realizing that only the pyloric and antral branches of the anterior vagal nerve are essential for normal gastric emptying[10] and that the posterior vagal trunk can be cut with impunity[11–13], he further simplified the procedure by combining an anterior lesser curve seromyotomy with posterior truncal vagotomy (ASPTV). Excellent initial results have been reported with this procedure[14]. Because it was specifically developed as a possible substitute for PGV, we decided to compare both procedures in a controlled clinical trial. We present a 2–5 year follow-up study with special attention to the clinical results and the reduction in pentagastrin-stimulated acid secretion.

Patients and methods

Ninety-one patients were admitted for elective surgery for uncomplicated chronic duodenal ulceration between April 1981 and April 1984 and have been included in this study, two were withdrawn. Duodenal ulceration has been demonstrated endoscopically in all patients. The indication for surgery was failed medical treatment whether or not combined with previous bleeding or perforation, or both. Sixty-four patients (ASPTV, $n=32$; PGV, $n=32$) were asymptomatic on H_2-antagonists but relapsed frequently off therapy. Twenty-three patients (ASPTV, $n=13$; PGV, $n=10$) judged their response to H_2-blockers insufficient. Their dyspeptic symptoms continued in spite of therapy. The two patients left, one from each group, did not receive H_2-blocking agents. Patients were excluded from the trial if they were undergoing surgery for complications of duodenal ulceration, or if they had any of the following: pyloric stenosis, combined gastric and duodenal ulcers, prepyloric ulcers or symptomatic, endoscopically proven oesophagitis. The operations were performed by consultants, senior registrars and registrars. The patients were assigned to either ASPTV or PGV by drawing a trial card from a box kept in the operating theatre. PGV was performed according to the technique described by Goligher[15], in which the lower 6 cm of the antrum was left innervated but the lower 5 cm of the oesophagus was denervated. ASPTV was performed according to Taylor's technique[14].

No intra-operative testing was used to assess the completeness of either procedure.

Gastric acid secretion

Acid secretory tests were performed after an overnight fast. The stimulated acid secretion was followed for 1·5 h after the intramuscular injection of 6 µg/kg of pentagastrin on an empty stomach, using 15 min collection periods. Peak acid output (PAO) was expressed as twice the sum of the acid outputs produced in the two highest consecutive 15 min periods. Before pentagastrin testing all acid inhibitory drugs, including H_2-blocking agents, were stopped for a period of at least 48 h. Pentagastrin tests were performed pre-operatively and 6 months postoperatively. All patients underwent pre-operative pentagastrin testing, 26 patients refused the test 6 months postoperatively, in spite of their previously given informed consent. Consequently, a complete acid secretion study was available for 63 patients (70·8 per cent, ASPTV, $n=33$; PGV, $n=30$).

Visick grading (clinical results)

The patients were interviewed by their consultant surgeon 1 month postoperatively. Thereafter, they were seen by one of the investigators (H. O.) at 3 and 6 months. Assessments of specific symptoms were recorded on a standard questionnaire.

Endoscopy was performed according to protocol at 6 months and if symptoms occurred. Twenty-two patients refused the gastroduodenoscopy 6 months postoperatively (24·7 per cent, ASPTV, $n=13$; PGV, $n=9$). At 12 months postoperatively and at yearly intervals thereafter, information was gathered by postal questionnaire. If the questionnaire revealed suspect symptoms, or the patient was not satisfied with the result at that time, he/she was asked to visit the outpatient clinic for further examination. The response to each questionnaire was decoded and scored in a uniform manner.

The Visick grading was assessed at 12 months postoperatively and at yearly intervals thereafter, using the modified classification of Goligher[16].

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Table 1 *Comparison of both groups of patients*

	ASPTV (*n*=46)	PGV (*n*=43)
Sex (M:F)	38:8	32:11
Median age (years)	44·0	42·0
Median ulcer history (months)	72 0	96 0
Previous complications		
Perforation	—	1
Haemorrhage	4	3
Pre-operative PAO (mean ± s.d.)	31·4 ± 12·1	32·9 ± 15·0

PAO, peak acid output. There was no significant difference between the two groups

Table 2 *Intra-operative and early postoperative sequelae*

	ASPTV (*n*=46)	PGV (*n*=43)
Splenectomy	1	—
Intraperitoneal bleeding	—	1
Bleeding ulcer	—	1
Wound infection	3	6
Pulmonary	4	4
Early dysphagia (<2 months)	19	24

A recurrent ulcer was defined as an endoscopically proven, symptomatic relapse Special attention was given to the presence or absence of early dysphagia, epigastric fullness, gastric retention, pyrosis, bile vomiting, dumping and diarrhoea, and classified as. absent, mild or severe A side-effect was considered severe if it interfered with the patient's life or necessitated repeated medication. Patients with diarrhoea were divided into two groups based on the frequency of the attacks: continuous diarrhoea and episodic diarrhoea.

Statistical analysis

Discrete variables were analysed by the Fisher Exact test and continuous variables were compared using the Mann–Whitney *U* test (only 2 by 2 comparisons were made). All comparisons were two-tailed and $P<0{\cdot}05$ was considered significant.

Results

Of the 91 patients who entered the study, 89 were followed up in accordance with the study protocol (PGV, $n=43$; ASPTV, $n=46$). Two patients were withdrawn: one patient from the ASPTV group underwent further surgery on the fifth and ninth postoperative days because of profuse bleeding from the duodenal ulcer and was treated by a truncal vagotomy with antrectomy; the other patient committed suicide 3 months after the operation (ASPTV group).

All but one of the patients (ASPTV) reported for the 1-year examination. Two years after the operation 83 questionnaires were returned by the patients for analysis (ASPTV, $n=45$; PGV, $n=38$).

The patients were well matched for sex ratio, age, duration of symptoms, previous complications of duodenal ulcer disease and pre-operative pentagastrin-stimulated PAO (*Table 1*). There was a significant difference in the duration of surgery: PGV mean 112·7 ± 31·0 min, ASPTV mean 56·4 ± 17·3 min, $P<0{\cdot}001$.

Mortality and complications

There were no postoperative deaths In one patient (ASPTV) a splenectomy had to be performed. Complications in the immediate postoperative period were similar for both groups of patients (*Table 2*).

Gastric secretion study

Pre-operative pentagastrin-stimulated PAO was 32·9 ± 15·0 mmol/h for the PGV patients and 31·4 ± 12·1 mmol/h for the ASPTV patients (*Table 1*). There was no difference in postoperative pentagastrin-stimulated PAO between the two groups (*Table 3*). The mean pentagastrin-stimulated PAO after surgery was 15·4 ± 9·5 mmol/h for the PGV group ($n=30$) and 16·3 ± 8·9 mmol/h for the ASPTV group ($n=33$). After PGV and ASPTV the mean reduction was 48·5 per cent and 50·5 per cent, respectively.

Visick grading

The classification was judged from the answers acquired from the standard surveys carried out at 1 and 2 years after the operation. Patients with a symptomatic, endoscopically proven recurrent ulcer were automatically graded Visick IV throughout. At the 1- and 2-year assessments no significant difference could be found between the two groups (*Table 4*).

At 2 years follow-up there were 32 (84·2 per cent) patients with a good result after PGV and 40 (88·9 per cent) after ASPTV. The result was poor in six (15·8 per cent) patients after PGV and in five (11·1 per cent) after ASPTV. Four patients were graded Visick III: recurrent symptoms without endoscopic confirmation (one from each group), gastric retention (PGV) and diarrhoea (ASPTV). The patients graded IV comprised seven with proven recurrent ulceration (ASPTV, $n=3$; PGV, $n=4$). Early dysphagia was observed in 24 patients after PGV (55·8 per cent) and in 19 patients after ASPTV (41·3 per cent) (*Table 2*). This symptom disappeared in all patients within 2 months.

Two patients underwent further surgery: one because of gastric retention (PGV) and one because of reflux oesophagitis (ASPTV). Except for the latter two patients, postoperative gastric sequelae, if present, were mild. They did not affect the patient's lifestyle or require medical treatment. No significant differences could be found between the two groups of patients (*Table 5*).

If diarrhoea was encountered, it was usually episodic and of a mild character, never affecting the lifestyle. Only two patients (ASPTV) did occasionally regard their bowel action as a problem. One of these needed medical treatment but did not find that the side-effect interfered with work or enjoyment of life to any great extent. Diarrhoea never led to the Visick IV classification.

Table 3 *Pentagastrin-stimulated acid secretion studies 6 months postoperatively*

	ASPTV (*n*=33)	PGV (*n*=30)
PAO (mmol/h)		
Mean ± s.d.	16·3 ± 8 9	15 4 ± 9·5
Median	16·8	14·1
Percentage reduction		
Mean ± s.d	50·5 ± 23·3	48·5 ± 26·3

PAO, peak acid output. There was no significant difference in postoperative PAO and percentage reduction

Table 4 *Visick grading of patients at 1- and 2-year follow-up*

Visick grade	1-year follow-up		2-year follow-up	
	PGV	ASPTV	PGV	ASPTV
I	21 (88·4%)	21 (84·4%)	15 (84·2%)	21 (88 9%)
II	17	17	17	19
III	4 (11 6%)	5 (15·6%)	2 (15·8%)	2 (11 1%)
IV	1	2	4	3
Total *n*	43	45	38	45

No significant difference was found between the two groups

Table 5 *Incidence of various procedure-related sequelae at 1- and 2-year follow-up*

	1-year follow-up		2-year follow-up	
	PGV	ASPTV	PGV	ASPTV
Epigastric fullness	5	6	6	6
Gastric retention	1 (1)	1 (1)	1 (1)*	1
Pyrosis	2	3 (1)*	2	2
Bile vomiting	1	2	1	1
Dumping	6	6	5	4
Diarrhoea				
Continuous	1	1 (1)	—	1 (1)
Episodic				
Mild	10	13	9	14
Severe	—	1 (1)	—	1

Values in parentheses are numbers of patients classified as Visick III because of these symptoms. * Patients requiring further surgery

Recurrences

At the time of writing (follow-up: median 36 months, range 24–60), the endoscopically proven, *symptomatic* recurrence rate for PGV and ASPTV was 9·3 per cent ($n=4$) and 8·7 per cent ($n=4$), respectively. The mean time interval between the operation and the endoscopically proven recurrence was 12 months after PGV (range 6–17) and 15 months after ASPTV (range 2–40). In the majority of cases the recurrence occurred within 18 months of vagotomy: this applied to all the patients after PGV and three out of five after ASPTV.

One patient had a persistent duodenal ulcer after ASPTV. Gastroduodenal endoscopy was carried out 2 months after the operation because of typical ulcer complaints. This revealed an unhealed ulcer. Medical treatment (H_2-antagonist) failed and the patient underwent further surgery 8 months postoperatively. On performing a truncal vagotomy and antrectomy it became obvious that the first acid-reducing operation must have been incomplete: a second posterior vagal structure was found (in all ASPTV procedures PTV was verified by a pathologist).

Fate of recurrences. Besides the patient already mentioned above, two others with a symptomatic recurrent ulcer underwent further surgery: one after PGV and one after ASPTV. The other five have been receiving maintenance doses of H_2-receptor blockers. Three of them have remained asymptomatic, while two have some dyspepsia occasionally.

Silent ulcers. At the 6 month endoscopy according to the protocol another two ulcers were encountered. Both patients, one from each group, were completely free of symptoms and not on medication, and have remained asymptomatic during the follow-up.

Subjective reaction on H_2-blockers. Considering both groups together, a significant difference in ulcer recurrence rate was found between the patients who were pre-operatively asymptomatic on H_2-blockers but relapsing frequently off therapy (total $n=64$: ASPTV, $n=32$; PGV, $n=32$) and patients who judged their response to H_2-antagonists insufficient (total $n=23$: ASPTV, $n=13$; PGV, $n=10$). In the former group three recurrences were encountered (4·7 per cent) whereas in the latter there were five recurrent ulcers (21·7 per cent) ($P<0{\cdot}05$).

Discussion

ASPTV was primarily developed to replace PGV, which is still not the procedure of choice in many surgical departments, partly because of its time-consuming character and technical difficulties Nevertheless, PGV combines an acceptable recurrence rate with very few adverse effects[1,2,7,8,17,18]. If any new operation is to replace PGV, it has to at least equal its results.

This study shows that ASPTV can be performed with fewer difficulties and in a shorter time than PGV. Although the gain in time might not be of such great importance, the simplicity of the operation is all the more so. It is common practice to treat patients with a duodenal ulcer medically, which means that fewer are referred for surgical treatment[19,20]. It is likely that an increasing number of surgeons will be less well-versed with the PGV technique, possibly resulting in a high rate of recurrent ulcers[8,18].

After ASPTV, the reduction in acid secretion was at least as good as after PGV. The reduction of pentagastrin-stimulated PAO after PGV in our series (48·5 per cent ± 26·3) corresponds well with figures found in the literature (mean 48 per cent; range 24–71)[17], suggesting that our technique of denervating the parietal cell mass using PGV is adequate and therefore allows comparison with the new procedure. Taylor[14] used insulin to stimulate acid secretion, which unfortunately makes comparison with our figures impossible. Satisfactory results, as shown by Visick grades I and II, were found in about 85 per cent of the patients after both procedures. Again, this corresponds well with figures found in the literature[2,7,17,18]. Procedure-related sequelae were seen in a minority of cases after both operations. A potential drawback of the new operation could have been a significantly higher incidence of diarrhoea. In spite of a rather meticulous search for this sequela, via specific questions in the survey, only two patients were encountered who incidentally took loperamide for relief of this phenomenon. The questions in the survey and the decoding system might easily be responsible for an overestimation of this symptom. This could explain the rather high incidence of mild episodic diarrhoea after both procedures. Neither Taylor[14], Hill and Barker[11], nor ourselves have seen patients with complaints of diarrhoea such as those often described after truncal vagotomy with drainage[21]. Evidence supporting the suggestion that the posterior vagal trunk does not play a key role in the development of postvagotomy diarrhoea has been found in the results of this study, the outcome of earlier non-randomized studies[11,14], the studies by Burge *et al.*[12] and by Smith and Farris[13] on selective vagotomy and in the study by Ladas *et al* [22] on postvagotomy diarrhoea.

Our data represent the cumulative rates of endoscopically proven symptomatic recurrent ulcers at 2–5 years postoperatively. After a median follow-up period of 3 years, four symptomatic recurrent ulcers were observed after PGV (9·3 per cent) and four after ASPTV (8·7 per cent). In the literature the mean symptomatic recurrence rate for PGV is 7–8 per cent after the same period (median 3 years; range 0·5–8 years)[17]. Although the incidence of symtomatic recurrent ulceration after PGV is well documented, data about asymptomatic recurrences are scarce. Müller and Martinoli found a total recurrence rate of 13·9 per cent after 5 years follow-up, while only 40 per cent of these (5·6 per cent) were symptomatic[17]. This figure was available because routine endoscopy (or barium meal) was part of the yearly follow-up protocol. In our study, a routine endoscopy was only performed at 6 months postoperatively. At that time, two out of five recurrent ulcers were asymptomatic (40 per cent; one from each group). Therefore the total recurrence rate in our series should be 11·6 per cent ($n=5$) after PGV and 10·9 per cent ($n=5$) after ASPTV. Nevertheless, in order to make our figures comparable to most other studies of PGV for duodenal ulcers, we used the symptomatic recurrence rate. The more so as figures of asymptomatic ulcers at more advanced intervals are missing.

Recurrence was more common in patients who judged the reaction to H_2-antagonists insufficient than in patients who were asymptomatic on H_2-blockers, confirming that ulcers healing on H_2-blocking agents do better after parietal cell vagotomy than ulcers that are resistant to this medical therapy[23].

Posterior truncal vagotomy is a critical step in the new operation and therefore received a great deal of attention in our description of the new operation[24]. The posterior vagal trunk is the one most frequently missed when performing truncal vagotomy[25]. In comparative studies, the recurrence rate after truncal vagotomy has been found to be three times as high as that following selective vagotomy[26,27]. This difference can only be explained by incomplete vagotomy in the truncal vagotomy procedure.

The results of ASPTV are promising at this stage in the follow-up (2–5 years). The operation is simple to perform, even in obese patients. It causes a reduction in acid secretion which is equal to that seen after PGV, apparently without the occurrence of additional procedure-related symptoms either as a result of the seromyotomy, or of the posterior truncal vagotomy. We therefore think that ASPTV is a good alternative to PGV in the surgical treatment of chronic duodenal ulcers.

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Stimulation of the healing of experimental colon anastomoses by low-power lasers

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Anastomotic leakage following colorectal surgery remains a complication with high mortality and morbidity. Recent studies suggest that helium–neon (He–Ne) lasers at specific energy densities can be used to enhance wound healing in different tissues. In this experimental study we have tested the strength of end-to-end anastomosis of the rat colon irradiated by He–Ne laser by measuring bursting pressures and bursting wall tensions at 2, 4 and 7 days after operation. The study shows that He–Ne laser radiation induces a significant increase in colonic strength at the anastomosis. The laser does not cause the luminal narrowing observed in non-irradiated specimens.

Keywords: Laser, wound-healing stimulation, colon anastomoses

Despite technical advances in the last decades, severe morbidity and approximately one-third of the deaths following colorectal surgery are caused by anastomotic leakage[1]. The reported incidence of clinical leakage for elective colonic surgery in many series is close to 14 per cent[2–4]. However, evidence from radiological and sigmoidoscopic assessment shows that anastomotic failure is more common than clinical assessment would indicate, with leak rates of 39–69 per cent for colorectal anastomoses[5].

Interaction of laser radiation with living tissue produces different effects, depending on the energy density (J/cm^2) applied[6] (*Table 1*). One of the lesser-known aspects of the use of lasers involves the possible biological effects of low-power (soft) lasers. These effects potentially modulate tissue metabolism in a selective non-destructive manner. The activation of metabolic processes and enzymatic induction with ruby and helium–neon (He–Ne) lasers has been described *in vitro*[7]: the effects include the stimulation of wound healing and tissue regeneration. These effects can be summarized as follows: (1) increase in collagen production, and fibroblast DNA and RNA synthesis[7–11]; (2) stimulation of new vessel formation[9,12,13]; (3) increase in tension resistance of the scar [9,14,15] and (4) stimulation of epithelialization[7].

Considering that these effects, if activated in the colon, could improve many of the factors involved in anastomotic failure, we have undertaken an experimental study of the effects of the He–Ne laser on the early stages of the healing of colonic anastomoses.

Materials and methods

Male Wistar rats (89), weighing 200–300 g were used The animals were anaesthetized with ether and a 3 cm midline incision of the abdominal wall was made The right colon was divided 1 cm distal to the proximal flexure[16], and an end-to-end inverting anastomosis was performed, using a single layer of interrupted stitches of 5/0 polyglycolic acid.

A total of 29 animals were used in the first phase of the study in order to determine the radiation dose which had most effect on anastomotic healing. Two regimens were tested: regimen A consisted of a 3-min intra-operative radiation dose (2·16 J/cm^2); regimen B consisted of a 5-min intra-operative radiation dose (3 6 J/cm^2) which was repeated on the second postoperative day. Both doses are within the range of well-established clinical and experimental patterns (2–4 J/cm^2) which have proved effective in wound healing stimulation[7,15,17,18]. After histological study of the scars, the best results were obtained with two doses of 3·6 J/cm^2 (F. Asencio and F. Martinez-Soriano, unpublished results), this treatment was used for the rest of the study The characteristics of the radiation according to Goldman[19] were: He–Ne laser; wavelength, 632 8 nm; beam power, 6 mW; type of emission, continuous; energy density, 3 6 J/cm^2.

The remaining 60 rats were randomly allocated to two groups of 30. In the first group (experimental) the anastomoses were irradiated with the above dose before laparotomy closure On the second postoperative day a second laparotomy was performed, the adhesions were divided and the anastomosis was irradiated again using the same dose In the second group (control) the same procedure was followed, but without irradiation

The rats were killed in series of 10 each at 2, 4 and 7 days after surgery. At autopsy a standard segment of colon 4 cm long including the suture line was excised. After the faecal content was milked out, the proximal end of the anastomosis was connected to an air-injecting perfusor (4·4 ml/min) by means of a polythene tube. The distal end was connected to a 0–300 mmHg pressure transducer, and the pressures were recorded by a polygraph The specimens were then immersed in saline at 37°C and inflated until the bowel leaked The site of leakage and maximum pressure reached (bursting pressure, *BP*) were recorded. Measurements of external bowel diameter, at the anastomosis and at 1 cm both proximal and distal to it, were carried out after leakage by means of a caliper[20–21].

Bursting wall tension (*BWT*) was calculated according to La Place's law: $BWT = BP \times r$ (references 23, 24). The measured diameters were converted into internal bowel radii (r) by division by two and subtraction of the wall thickness

The index of narrowing at the anastomosis (*NI*) is given by the formula $100(1–2A/B+C)$, where A is the diameter at the anastomosis, B the diameter 1 cm proximally and C 1 cm distally Thus an index of 100 represents complete stenosis and an index of 0 means no narrowing[2,23].

Statistical analysis for all experiments was performed by Student's t test.

Results

All rats survived until the day they were killed. There was no evidence of peritonitis or spontaneous free anastomotic leakage in any rat. Nevertheless we observed covered dehiscence at the time of division of adhesions on the second postoperative day in one animal in the irradiated group and in four of the controls. These animals were not included in the experiment.

Bursting pressures

At 7 days. *Tables 2* and *3* show the values (mean and s.d.)

Table 1 *Effects of lasers on living tissues*

	Energy density (J/cm^2)
Biostimulation	<4
Biosuppression	>4
Cytotoxicity	40
Thermal effects	400–4000

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Table 2 *Manometric results from irradiated animals at day 7*

Rat	Colon diameter* (cm) *B*	*A*	*C*	Site of rupture†	*BP*‡	Internal radius (cm)	*BWT*§	*NI*¶
1	1·3	1·1	1·1	c	148	0·40	78·7	8·3
2	1·1	1	0·9	c	154	0·35	71·7	0
3	1·2	1·1	1	a	150	0·40	79·8	0
4	1·1	0·9	1	c	184	0·30	73·4	14·28
5	1·1	1	0·9	c	168	0·35	78·2	0
6	1·2	1	1·1	a	170	0·35	79·1	13·04
7	1·1	1·1	1·1	c	184	0·40	97·9	0
8	1·2	1·1	1·1	a	186	0·40	98·9	4·34
9	1·2	1·1	1	a	176	0·40	93·6	0
10	1·1	1·1	1	c	162	0·40	86·2	−4·76
x̄	1·16	1·05	1·02		168·2	0·375	83·75	3·486
s.d.	0·07	0·07	0·08		14·4	0·035	9·88	6·324

* Diameter *A* at the anastomosis; *B*, 1 cm proximal; *C*, 1 cm distal; † Rupture a, at the anastomosis; c, outside the anastomosis; ‡ *BP*, bursting pressure; § *BWT*, bursting wall tension, ¶ *NI*, narrowing index

Table 3 *Manometric results from controls at day 7*

Rat	Colon diameter (cm) *B*	*A*	*C*	Site of rupture	*BP*	Internal radius (cm)	*BWT*	*NI*
11	1·2	1	1·2	a	166	0·35	77·3	16·66
12	1·2	1	1·1	a	168	0·35	79·1	13·04
13	1·3	1	1·1	a	140	0·35	65·2	16·66
14	1·2	1	1·1	a	146	0·35	69·4	13·04
15	1·5	1·2	1·4	c	112	0·45	67·0	17·24
16	1	0·9	1	a	160	0·30	63·8	10·00
17	1·1	0·9	1	a	155	0·30	61·8	14·30
18	1·3	1·1	1·2	a	153	0·35	71·2	12·00
19	1·1	1	1·1	a	151	0·35	70·3	9·09
20	1·2	1·1	1·1	a	146	0·35	67·9	4·34
x̄	1·2	1·0	1·1		153·9	0·35	69·3	12·6
s.d.	0·1	0·1	0·1		18·1	0·04	5·5	4·5

Abbreviations and symbols as in *Table 2*
Probabilities (irradiated *versus* controls): BP, $P<0{\cdot}05$, internal radius $P<0{\cdot}5$ (n.s.); *BWT* $P<0{\cdot}01$; *NI* $P<0{\cdot}01$

for bursting pressures and narrowing indices in the irradiated and control groups. Rupture occurred outside the anastomosis in six of the irradiated rats compared with one of the control animals. At this healing stage, the anastomoses from the irradiated group showed a significantly increased resistance to pressure when compared with the control group ($P<0{\cdot}05$ for *BP* and $P<0{\cdot}01$ for *BWT*).

At 4 days. Rupture occurred at the anastomosis in all cases. The mean values of *BP* (52·1; s.d. = 16) and *BWT* (22·4; s.d. = 8) in the irradiated group were greater than in the controls (*BP* = 48·3; s.d. = 10·5 and *BWT* = 19·1; s.d. = 4·1), but this difference was not of statistical significance.

At 2 days. All cases also ruptured at the anastomotic site. The pressure values were substantially similar in both groups.

Figures 1 and *2* show the changes in *BP* and *BWT* in relation to time, and demonstrate an increased resistance to air inflation as time passes, with a rapid gain in strength between days 4 and 7.

Anastomotic narrowing

The degree of narrowing expressed as the index of narrowing was lower in the irradiated group at 7 days (3·5 ± 6·3) than in the controls (12·6 ± 4·5), this difference being statistically significant ($P<0{\cdot}01$). At 4 days, the NI of the irradiated anastomoses (7 ± 5·4) remained significantly lower than that of the controls (16·3 ± 8·5) ($P<0{\cdot}02$).

Discussion

The healing of colon anastomoses irradiated by low-power He–Ne laser was examined between the second and seventh postoperative day by determination of the bursting strength. This method has become a standard procedure in assessing colonic healing in the rat[2,23–31]. Bursting strength can be expressed either as bursting pressure (*BP*), i.e. the intraluminal pressure at leakage, or as bursting wall tension (*BWT*), which expresses circular wall tension at the point of rupture. It has been suggested[21] that *BWT* gives a more accurate measurement of bursting strength. However, comparison of both parameters in our study has shown a good correlation between the two, due to the fact that there were only small variations in the calculated radii among the different subgroups. The values of *BP* and *BWT* in our study are quite comparable to those obtained by others[32–34].

Most authors[20,25,31,33] describe similar changes in the mean colonic bursting pressures during the postoperative period. The seventh postoperative day is considered as the time of definitive joining of the bowel ends, as *BP* of the colon remains fairly constant from the seventh to the fourteenth day. During the first 4 days, the edges of the wound are held together only by sutures[34]. Bursting strength measurements revealed a significant difference between irradiated and control animals on the seventh postoperative day, when presumably anastomotic resistance is no longer dependent upon the sutures.

Although significant differences have been observed between the control and laser-exposed colons, the fact that over one-half of the irradiated anastomoses healed more strongly than the adjacent colon by 7 days, compared with only one for the control group, emerges as the most significant result of the

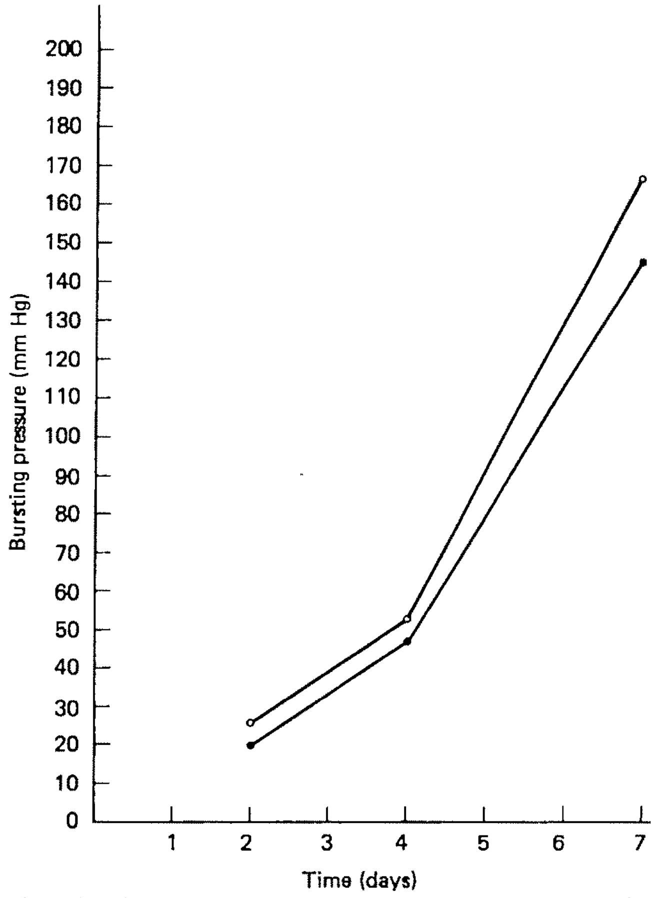

Figure 1 *Changes in mean colonic bursting pressures* (BP) *during the postoperative period;* ●, *controls;* ○, *irradiated,* P>0·01

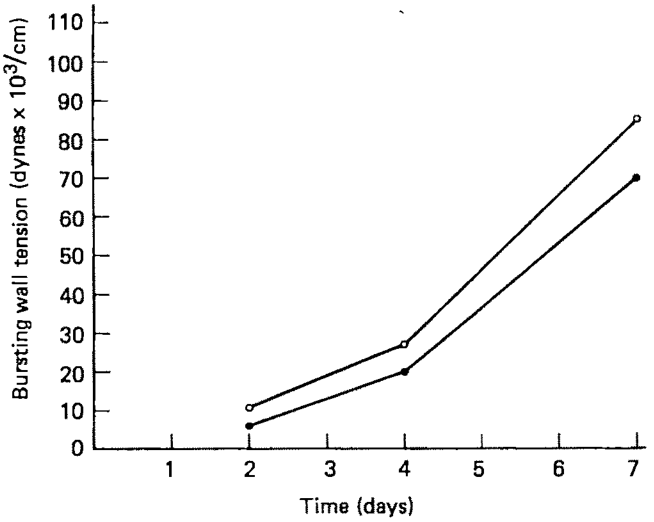

Figure 2 *Changes in mean colonic bursting wall tensions* (BWT) *during the postoperative period*, ●, *controls*, ○, *irradiated*; $P>0{\cdot}01$

study. Nevertheless, the development of a resistant circular scar will have positive effects only if, at the same time, it does not produce an excessive narrowing of the intestinal lumen: such narrowing does not seem to occur in the irradiated anastomoses.

Our results agree with the studies by Surinchak *et al.*[14] and Hutschenreiter *et al.*[15], who observed an increase in tensile strength in laser-stimulated skin wounds. The same effect was not found in wounds irradiated with incoherent light of the same wavelength. Abergel *et al.*[8] observed a dramatic enhancement of procollagen production following He–Ne laser irradiation in human fibroblast cultures that initially showed very low levels of collagen production. This observation opens the possibility of greater stimulation of the healing of colonic anastomoses in patients with an impaired wound-healing capacity who consequently have a greater risk of anastomotic leakage.

The very rapid healing rate of colonic wounds compared with that of other tissues[35], thus diminishing the need for multiple exposures to radiation and the accessibility of low rectal anastomoses to repeated laser irradiation, suggests that low-power lasers might reduce the incidence of clinical leakage following large-bowel anastomosis. Further data are needed to determine whether these experimental results can be translated to a clinical context.

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Low molecular weight heparin compared with unfractionated heparin in prevention of postoperative thrombosis

M. Samama, P. Bernard, J. P. Bonnardot, Sophie Combe-Tamzali, Y. Lanson and E. Tissot, on behalf of the participants of the Groupe d'Etude de l'Enoxaparine (GENOX) multicentric trial*

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Three consecutive randomized open studies have been carried out to determine the optimal dosage of low molecular weight heparin (LMWH) in the prevention of postoperative thrombosis in general surgery (892 patients). All patients undergoing abdominal, gynaecological, thoracic or urological surgery were over 40 years old and presented at least one of the following risk factors for thrombosis: previous thromboembolism, obesity, varicose veins, malignancy (30 per cent), pre-operative hospitalization over 5 days, oestrogen therapy, chronic cardiac disease or bronchitis. Isotopic venous thrombosis and bleeding complications were assessed after subcutaneous administration of a LMWH fragment (LMWH, Enoxaparine) or unfractionated heparin (UH). The three studies compared 3 × 5000 units UH daily with 1 × 60 mg, 1 × 40 mg, 1 × 20 mg LMWH daily. Thromboembolic events rates were not significantly different from group to group (UH: 3·8 per cent, 2·7 per cent, 7·6 per cent respectively compared with LMWH: 2·9 per cent, 2·8 per cent, 3·8 per cent). Bleeding episodes including wound haematoma formation, perioperative blood losses and systemic haemorrhage were not significantly different in patients receiving LMWH or UH. Significant decreases in haematocrit and haemoglobin were only observed in patients receiving 60 mg Enoxaparine (as compared to UH). An analysis using the 'intention to treat' approach gave results consistent with those of an analysis of good compliers. An overview of isotopic thromboses in the three studies gave no evidence of differences amongst the effects of the three doses of LMWH (P = 0·20), and pooling the results of the three studies using the Mantel–Haenszel procedure gave no evidence of a global difference between Enoxaparine and UH (P = 0·54). These results suggest that an optimal dosage of 20 mg/day of Enoxaparine is safe and effective in the prevention of postoperative thrombosis in this population.

Keywords: Unfractionated heparin, low molecular weight heparin, postoperative thrombosis

Two international studies[1,2] have reported that a single daily subcutaneous injection of low molecular weight heparin (LMWH), CY216 (Fraxiparine®, Choay, France) or Kabi2165 (Fragmin®, KabiVitrum, Sweden), is at least as effective in preventing postoperative deep vein thrombosis (DVT) as unfractionated heparin (UH). The expected beneficial effects were not completely achieved in the second study[2] because of an unexpected incidence of haemorrhagic complications. Both studies have used a single dose regimen of LMWH. In contrast, UH was given twice a day.

We carried out three consecutive open randomized trials on a total of 892 patients to compare three different dose regimens of LMWH (Enoxaparine, Lovenox®, Pharmuka, France) with UH (5000 units three times a day) in the prophylaxis of DVT and to determine the incidence of haemorrhagic complications in each regimen. These trials were conducted consecutively in order to determine the best risk:benefit ratio.

Patients and methods

A total of 892 patients over 40 years of age, scheduled to undergo general surgery of more than 45 min duration under general anaesthesia, and presenting at least one of the following risk factors: previous thromboembolism, obesity, varicose veins, malignant disease, pre-operative hospitalization over 5 days, oestrogen therapy, chronic cardiac disease or bronchitis, were studied at one centre or more among the ten participating ones.

The following characteristics were exclusion criteria of the study: heparin or iodine hypersensitivity, impaired renal function, haemorrhagic diathesis, current treatment with anticoagulants, thyroid dysfunction, recent myocardial or cerebral infarction (< 6 months) and pregnancy. In the third trial, intra-operative blood loss over 40 per cent of blood volume (> 8 units of blood transfused) was also an indication for exclusion. We considered that such blood losses, obviously related to the surgical procedure, might introduce a bias in the evaluation of the bleeding due to the treatment itself.

Patients gave their informed consent before entering the study.

Prophylactic regimen

Each study was performed as an open trial, comparison being made between two randomized prophylactic groups, one receiving LMWH and the other UH. The treatment groups were further named: group A (60 mg LMWH compared with UH), group B (40 mg LMWH compared with UH), and group C (20 mg LMWH compared with UH).

Conventional low-dose UH groups. Heparin 5000 units was given subcutaneously 2 h before operation, and then every 8 h for the next 7 days.

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* *See Appendix for Genox clinical centres*

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Heparin fragment groups. The LMWH groups received either Enoxaparine 60 mg, 40 mg or 20 mg given subcutaneously 2 h before surgery and then every morning for 7 days.

Drugs used

LMWH fragment. Enoxaparine is a sodium salt of benzylic ester of heparin, obtained by a partially controlled depolymerization procedure. Anti-Xa amidolytic activity is about 110 units/mg as compared to the 4th International Heparin Standard.

Unfractionated heparin. A calcium salt of a commercial preparation of porcine mucosal origin

Assessment

Screening for development of postoperative deep vein thrombosis was made using the ^{125}I-labelled fibrinogen uptake test, with injections of 100 μCi of fibrinogen (Amersham, UK) after thyroid block with KI or NaI. Measurements were made on the first postoperative day and every second day thereafter except when there was an increase in uptake, in which case measurements were made daily. An increase in uptake of 20 per cent or more for at least 24 h between two adjacent points in the same leg, or between the same points in both legs, was considered diagnostic evidence of deep vein thrombosis. The fibrinogen screening was continued for 7 days. Ascending phlebograms were not usually performed if the patient had raised counts, because the diagnostic endpoint was the ^{125}I test. Any clinically suspected pulmonary embolism had to be confirmed by lung scanning or angiography.

Recording of complications

Intra-operative bleeding was measured by anaesthetists by counting units of blood transfused during surgery. All postoperative bleeding, wound haematomas, reoperations, and postoperative transfusion requirements were also counted. Allergic side effects as well as local complications at the injection site were noted.

Laboratory analysis

Blood samples were taken before the first injection and on postoperative days 1, 2 or 3, 4 or 5, 6 or 7 at 3 h after Enoxaparine injection, and 4 h after UH injection. The following tests were made: red cell and white cell counts, platelet count, haemoglobin and haematocrit (Coulter S® apparatus); activated partial thromboplastin time (using different commercial reagents); Factor Xa inhibitor activity (amidolytic assay).

Statistical methods

In a first step we performed an analysis based on 'intention to treat', counting all the included patients. 'Failure' status was assigned to patients who for any reason could not be followed up until the end of the trial. The standard statistical tests used for comparing the two treatment groups in each study were the χ^2 test and Fisher's exact test. A second analysis was done on those patients with whom the protocol requirements were fully met.

In a third step the results of the three studies were pooled using the Mantel–Haenszel procedure. A confidence interval was obtained for the pooled odds ratio using an approximation to the distribution of the log odds ratio.

Results

Seven patients were excluded from the trials because the protocol was not followed exactly. In one case the surgery lasted less than 30 min; in one case the patient had a pre-existing abnormality of haemostasis; and in five cases one or more wrong additional doses of LMWH were given. The 885 remaining patients received the following prophylaxis: group A (304 patients) Enoxaparine 60 mg, 157; UH, 147; group B (247 patients) Enoxaparine 40 mg, 124; UH, 123; and group C (334 patients) Enoxaparine 20 mg, 167; UH, 167.

Although 885 patients entered the trial, some of them were dropped from the study for various reasons (*Table 1*). The analysis of safety with regard to excessive bleeding included all patients even if fibrinogen uptake test was inadequate. In the third study, four patients were excluded from analysis because of the supplementary criterion (transfusion requirement of more than 8 units of blood). Three of these patients had received UH 5000 units pre-operatively, and one was in the Enoxaparine 20 mg group. These four underwent either cystectomy or cystoprostatectomy.

In the three trials the LMWH and UH groups were well matched for: age (years), 54·3±0·9/54·7±0·9 in group A, 55·8±11·1/55·8±11·4 in group B, 60·3±11·2/59·1±11·1 in group C; sex ratio M:F, 32:128/35:112 in group A, 34:93/28:95 in group B, 59:109/67:100 in group C; duration of surgery (min), 162±5/175±7 in group A, 166±75/160±78 in group B, 150±81/143±80 in group C; and the presence of risk factors, except in group B where the frequency of oestrogen therapy and obesity was significantly higher in patients receiving 40 mg Enoxaparine compared with the control group ($P=0{\cdot}02$ and 0·04).

There was no difference between LMWH and UH groups in each trial in terms of percentage of patients with malignant diseases. However, thoracic surgery was performed in two trials only, and the urological surgery population was larger in the last trial.

In group A both treatments were equally effective in preventing postoperative isotopic venous thrombosis (3 per cent with Enoxaparine and 3·8 per cent with UH). Phlebography was performed in only four of the nine cases in which the ^{125}I fibrinogen test was positive. Two out of four phlebograms were abnormal (one in each treatment group). One clinically suspected pulmonary embolism occurred in the UH group. This diagnosis was supported by a positive scintigraphic lung scan. The ^{125}I fibrinogen test remained negative. The percentage of patients transfused, the number of units transfused, the amount of blood collected by drainage and the number of wound haematomas were identical in the two patient groups. On the other hand, there were four patients with systemic haemorrhagic complications in the 60 mg Enoxaparine group who required withdrawal from further treatment, and reoperation was required in one of these. In the control group UH was discontinued in one patient out of the three who had a systemic haemorrhage. The biological measurements of blood loss were higher in the Enoxaparine group than in the control. The decrease in red cell count, haemoglobin and haematocrit could only be reasonably assessed in non-transfused patients and was significant ($P=0{\cdot}03$).

In group B the percentage of isotopic thrombosis was identical (2·8 per cent) in the two groups. Two phlebograms

Table 1 *Reasons for exclusion from efficacy analysis (in good compliers only)*

	Group A		Group B		Group C	
	LMWH 60*	UH	LMWH 40*	UH	LMWH 20*	UH
No. of patients	157	147	124	123	167	167
Inadequate fibrinogen uptake test because of:						
Technique	15	13	13	11	3	7
Reoperation	0	0	1	0	3	0
Premature discharge	0	0	1	0	1	0
Death	2	0	1	0	1	0
Haemorrhage and end of treatment	3	1	1	2	0	2
Premature end of treatment	0	0	1	0	1	0
Total of patients included for efficacy criterion	137	133	106	110	159†	158

LMWH, low molecular weight heparin; UH, unfractionated heparin; * daily dose of LMWH in mg. † The patient whose treatment ended prematurely also underwent reoperation were performed in two of the three patients receiving UH who developed a positive ^{125}I fibrinogen test. They were both abnormal. None were performed in the three patients from the Enoxaparine group with an abnormal ^{125}I test. No pulmonary embolism occurred in either group. No significant difference was found using the same criteria for general tolerance in the two groups. With regard to blood count, the decrease in red cell count, haemoglobin and haematocrit was significant in relation to pre-operative values in each group, but not between the two treatment groups.

In group C the reduced dose regimen of Enoxaparine 20 mg was as effective as the larger dose (3·7 per cent isotopic thromboses) and still comparable to the results with unfractionated heparin (7·6 per cent). General tolerance was equally good in both patient groups.

Mortality rate

Four patients died. They all received Enoxaparine. Three of them had malignant disease (*Table 2*).

Biological results

Activated partial thromboplastin time and cell counts did not differ between the groups at any dosage and at any time, except for red cell counts when a dosage of 60 mg Enoxaparine was used. Postoperative anti-Xa activities were: 5·1 ± 1·9, 3 ± 1·2, 1·28 ± 0·7 µg/ml of plasma for patients receiving 60, 40, 20 mg of Enoxaparine. In contrast, activities in patients treated with UH were < 0·1 ± 0·1 units/ml of plasma (P=0·03). Thrombocytopenia did not occur in any group. The patients with a decrease in platelet count were those who had been transfused with several units of red cell concentrate.

Table 2 *Causes of death*

Patient	Dosage of Enoxaparine	Diagnosis	Cause of death
Man (56 years)	60 mg	Lung cancer	Cardiac failure on Day 4
Man (73 years)	60 mg	Lung cancer	Cardiac failure during reoperation because of bleeding on Day 1
Man (72 years)	40 mg	Lung cancer	Cardiac failure on Day 1. Autopsy. no haemorrhage, no pulmonary embolism
Man (63 years)	20 mg	Megalo-oesophagus	Reoperation on Day 3 (peritonitis) Death on Day 5

Discussion

These trials were not performed in a double-blind fashion because this was the first study of Enoxaparine in general surgery. However, randomization of patients at entry and objective criteria of effectiveness and of general tolerance (haemorrhagic side-effects) permit reasonable conclusions to be drawn from an open study.

Effectiveness

The optimum dose of LMWH to prevent postoperative DVT remains to be established. In previous studies[1-4] LMWH was compared with two doses/day UH. It is generally accepted that prophylaxis with three doses/day is more effective than two doses[5]. One could argue that although one dose/day LMWH was effective when compared with two injections of UH[1,2], it could be less effective than the conventional Kakkar regimen of 5000 units thrice daily. In these three consecutive trials we decided to test the dose of Enoxaparine corresponding to an anti-Xa activity of 5000 units UH three times daily, also taking into account the higher bio-availability of Enoxaparine.

The fall in blood count observed in group A with 60 mg Enoxaparine led to trials with lower doses. The lower doses did not lead to a significant difference in prophylaxis benefit between LMWH and conventional low-dose heparin treatment. If the analysis is based on 'intention to treat', failures being assigned to patients who could not be followed up for any reason until the end of the trial, no difference is observed between LMWH and UH groups. In each trial the percentages of isotopic thrombosis are: 17 per cent and 13 per cent (27/160 and 19/147) in group A, 19 per cent and 13 per cent (24/127 and 16/123) in group B, 9 per cent and 13 per cent (15/168 and 21/167) in group C, differences which are not significant (*Table 3*). Pooling these results using the Mantel–Haenszel procedure showed consistent results for the three doses of LMWH and revealed no significant difference between LMWH and conventional heparin: χ^2=0·38, d.f.=1, P=0·54, odds ratio=1·15 (95 per cent confidence interval 0·77–1·71).

If the analysis is based on patients treated exactly according to the protocol, the frequencies of postoperative thrombosis for Enoxaparine and UH are respectively: 2·9 per cent and

Table 3 *Clinical data*

	Group A		Group B		Group C	
	LMWH 60*	UH	LMWH 40*	UH	LMWH 20*	UH
Clinical events in good compliers:						
Positive leg scan/performed tests (%)	4/137 (2·9)	5/133 (3·8)	3/106 (2·8)	3/110 (2·7)	6/159 (3·8)	12/158 (7·6)
Clinical events in all patients:						
Method on 'intention to treat' (failures were assigned for patients who could not be followed up until the end of the trial) for any reason (%)	27/160 (17)	19/147 (13)	24/127 (19)	16/123 (13)	15/168 (9)	21/167 (13)
Positive venograms/venograms performed	1/2	1/2	0/0	2/2	1/1	0/1
Pulmonary embolism (lung scan)	0	1	0	0	0	0
Tolerance data						
Percentage of transfused patients (%)	51·6	48·3	42·3	43·9	44·5	36·5
Number of units transfused	3·5 ± 0·36	3·7 ± 0·48	2·8 ± 1·9	3·2 ± 3	3·9 ± 2·2	3·2 ± 2·3
Mean postoperative drainage (ml)	230 ± 35	253 ± 37	247 ± 446	278 ± 559	308 ± 486	294 ± 364
Wound haematoma	15	16	10	15	1	4
Haemorrhage	4	3	2	2	3	4
Prophylaxis discontinued	4	1	0	1	1	3
Reoperation due to bleeding	1	1	1	0	1	1

LMWH, low molecular weight heparin, UH, unfractionated heparin; * daily dosage of LMWH in mg

3·8 per cent in group A (4/137 and 5/133) ($P=0{\cdot}7$), 2·8 per cent and 2·7 per cent in group B (3/106 and 3/110) ($P=0{\cdot}95$), 3·8 per cent and 7·6 per cent in group C (6/159 and 12/158) ($P=0{\cdot}14$), differences which are not significant (*Table 3*). Pooling these results using the Mantel–Haenszel procedure showed consistent results for the three doses of LMWH: $\chi^2=0{\cdot}76$, d.f.$=2$, $P=0{\cdot}68$. There was a trend towards a benefit for LMWH (odds ratio 0·64, s.e.m. 0·36), although this was not significant: $\chi^2=1{\cdot}16$, d.f.$=1$, $P=0{\cdot}28$.

It is, however, important to note that, although the majority of characteristics in groups A, B and C remained homogeneous for each treatment, the types of surgery were different: firstly, 58 per cent of surgery was gynaecological in group A, 54 per cent in group B, but only 26 per cent in group C; secondly, the thoracic surgery centre withdrew from the last trial and finally, urological surgery constituted 7·5 per cent of patients in group A, 9 per cent in group B, and 36 per cent in group C.

In group C we observed an increase in positive ^{125}I fibrinogen tests compared with the results in groups A and B (18, 9 and 6 respectively). In this group, the proportion of patients older than 60 years is higher than in groups A and B. Moreover the subgroup of patients who underwent urological surgery is larger (36 per cent). In this population the number of positive ^{125}I fibrinogen tests is 0/62 for patients receiving 20 mg of Enoxaparine and 5/60 for those receiving three subcutaneous injections of UH ($P=0{\cdot}06$ Fisher test two tails exact). The rate of malignancies in both subgroups is the same. These results suggest good efficacy of LMWH in urological surgery. This finding is important since the efficacy of UH is not fully established in this high risk group[5,6]. In group C, 16/18 patients with a positive leg scan were older than 60 years.

Tolerance

The safety of subcutaneous unfractionated heparin treatments is still debated because of the increased incidence of postoperative wound haematoma[7]. In this study the analysis did not reveal any significant difference between the two products. There was no significant difference either between the groups in terms of postoperative blood loss as measured by drainage (ml): 230±35 and 253±37 in group A, 247±446 and 278±559 in group B, 308±486 and 294±364 in group C, or in the amounts transfused (units): (3·5±0·36 and 3·7±0·48 in group A; 2·8±1·9 and 3·2±3 in group B; 3·9±2·2 and 3·2±2·3 in group C).

There was no statistically significant difference between the UF heparin groups and LMWH groups in numbers of wound haematomas: 15 and 16 in group A, 10 and 15 in group B, 1 and 4 in group C (*Table 3*). However, in one centre of group B which included 14·4 per cent of the total of patients, we can observe a 'centre effect': 33 per cent of patients included in this centre had a wound haematoma and they represented 48 per cent of the total wound haematomas in group B (12/25). The higher incidence of wound haematoma in gynaecological patients observed in one of the previous trials[1] was not observed in this study. There was no statistically significant difference in the systemic haemorrhagic complications among the groups (*Table 3*). However, lower doses of Enoxaparine were associated with a reduced frequency and severity of systemic haemorrhage, and therefore of treatment interruption.

The frequencies of ecchymoses at the injection sites were always significantly higher with three injections of UF heparin than with one injection of Enoxaparine, regardless of dose.

We conclude that the optimal dose regimen of Enoxaparine in general surgery seems to be 20 or 40 mg; 20 mg was found to be as effective as 5000 units UH thrice daily. This finding is important because Enoxaparine is compared with the effective regimen proposed by Kakkar for prevention of postoperative DVT. In subgroup analysis the regimen with Enoxaparine gave encouraging results following urological surgery and in patients with malignancy and/or older than 60 years. The plasma anti-Xa amidolytic activity 3–4 h after injection was significantly higher in patients receiving Enoxaparine than in those treated with UH. The clinical and biological tolerance of this LMWH was similar to that of UH. Thus Enoxaparine could represent an advance in prophylaxis of postoperative DVT because of its good risk–benefit ratio and a reduced number of injections, due to its better bio-availability[8,9].

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Appendix

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Cytotoxic-loaded albumin microspheres: a novel approach to regional chemotherapy

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Adriamycin®-loaded albumin microspheres (15–40 μm diameter) incorporating 1 per cent by weight of Adriamycin were prepared by cross linking albumin with glutaraldehyde. After systemic administration in rats, the microspheres were trapped in the pulmonary capillary bed, biodegradation occurring over 48 h. After selective intrarenal arterial injection of ^{99m}Tc-labelled albumin microspheres in rabbits, 97 per cent of the injected microspheres were trapped within the kidney; less than 1 per cent were found in the contralateral kidney, lungs and liver. Similar results were obtained after selective intrahepatic arterial injection. The selective injection of cytotoxic-loaded microspheres may provide a reliable method of administering high concentrations of cytotoxic drug to a target organ without producing high serum levels; this technique may have a role in the management of solid tumours.

Keywords: Oncology, chemotherapy

The results of systemic cytotoxic therapy in many solid tumours have proved disappointing. Most antineoplastic agents have steep dose–response curves and attempts to increase the therapeutic effect by escalating dosage have been accompanied by unacceptable systemic toxicity. As a result there has been some interest in the concept of regional chemotherapy, based on the premise that increased drug exposure within the tumour-bearing region would be accompanied by low serum levels and minimal toxicity. A further development of this concept is the use of radioactive microspheres[1] or biodegradable starch microspheres[2] which may be co-administered with cytotoxic drugs.

We have recently developed Adriamycin-loaded albumin microspheres (15–40 μm diameter) which, in theory, if administered intravenously or by selective intra-arterial injection, should be trapped in the first capillary bed encountered. Release of drug by diffusion and biodegradation of the albumin matrix should then occur producing a high drug level in the target organ with minimal systemic exposure.

The aim of the present study was to evaluate the extent of entrapment of albumin microspheres after intravenous, intrarenal arterial and intrahepatic arterial administration in animals.

Materials and methods

Preparation of Adriamycin-loaded albumin microspheres

Adriamycin-loaded albumin microspheres were prepared by adding an aqueous solution (1 ml) containing 20 per cent bovine serum albumin, 1 per cent Adriamycin and 1 per cent glutaraldehyde to a constantly stirred 60:40 mixture of cotton seed oil and petroleum ether, to form a water-in-oil emulsion[3]. The disperse aqueous phase containing the albumin and Adriamycin was stabilized by cross linkage of protein with glutaraldehyde. The resultant microspheres, containing approximately 1 per cent Adriamycin on a weight for weight basis, were washed in petroleum ether and isopropanol and reconstituted in phosphate-buffered saline containing 0·5 per cent Tween 80 After mesh filtration and differential centrifugation microspheres of 15–40 μm diameter (50 per cent weight average) were obtained. On dark ground illumination the natural orange-yellow colour of Adriamycin can be clearly demonstrated within the albumin microspheres (*Figure 1*).

Organ microsphere entrapment

Intravenous injection. Under halothane anaesthesia Adriamycin-loaded albumin microspheres (3–4 mg) were injected into the tail vein of male Wistar rats. The rats were then killed at 1 h ($n=3$) and 24 h ($n=3$) After exsanguination the lungs were examined histologically to assess the distribution of microspheres.

Selective intrarenal arterial injection. Under halothane anaesthesia, and under direct vision, polythene cannulae were placed in the right renal artery and inferior vena cava of male New Zealand white rabbits (2 kg weight) and ^{99m}Tc-labelled albumin microspheres (2·5 mg, 1 mCi/10 mg protein) were injected directly into the right renal artery. After 1 h a 1 ml blood sample was obtained. The animal was killed and both kidneys, liver and both lungs were removed. The tissue was homogenized and counted in tandem with appropriately diluted ^{99m}Tc microsphere standards in a Geiger-Müller tube. The degree of organ entrapment was expressed as organ c.p.m. ÷ total recovered c.p.m. × 100 per cent.

The distribution of microspheres within the renal parenchyma was assessed histologically. A portion of the right kidney was fixed in 10 per cent buffered formalin, the remaining tissue frozen in liquid nitrogen. Formalin-fixed material was embedded in paraffin wax, sectioned and prepared with Masson stain. The frozen material was sectioned in a cryotome and mounted in uvinert for fluorescent microscopy (Polyvar Fluorescent Microscope, excitation $\lambda=468$ nm, emission $\lambda=550$ nm).

Selective intrahepatic artery injection. In a similar manner the hepatic artery was cannulated in anaesthetized New Zealand white rabbits After injection of ^{99m}Tc-labelled albumin microspheres the animal was killed and the liver, lungs and kidneys removed, homogenized and the uptake measured in a Geiger-Müller tube. The degree of organ entrapment was again expressed as a percentage of the total radioactivity recovered.

Results

Intravenous administration

One hour after intravenous administration the Adriamycin-loaded albumin microspheres were visualized on light microscopy trapped within the alveolar capillary bed (*Figure 2*);

Table 1 *Distribution of radiolabelled microspheres after selective intrarenal arterial injection*

R. kidney	L. kidney	Liver	Lung	Blood (per litre)
97±5	0·3±0·1	0·6±0·3	0·2±0·2	1·9±1·7

Results are expressed as a percentage of the total count and are presented as mean±s.d. ($n=5$)

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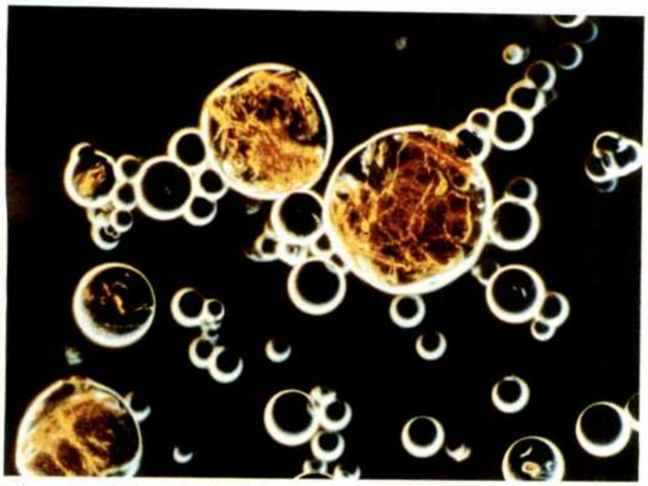

Figure 1 *Adriamycin-loaded albumin microspheres on dark ground illumination*

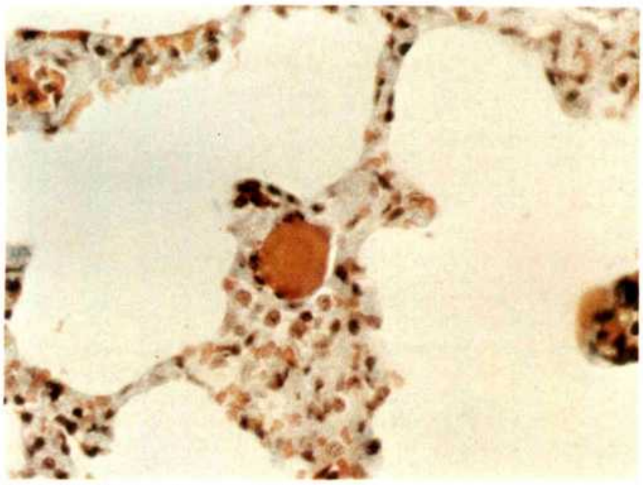

Figure 2 *Microspheres trapped in rat lung*

24 h after injection, partial destruction and ingestion of microspheres by macrophages was noted.

Selective intrarenal arterial injection

One hour after selective right renal arterial injection of ^{99m}Tc-labelled albumin microspheres over 95 per cent of the injected microspheres were trapped within the right kidney; less than 1 per cent were found in the contralateral kidney, lungs and liver (*Table 1*). On histological examination of the right kidney microspheres were seen in small arteries and arterioles down to the level of the glomerular capillaries (*Figure 3*). It was also possible to examine Adriamycin distribution by fluorescent microscopy. Adriamycin fluoresces orange-red and could be seen within the microspheres, trapped in renal arterioles.

Selective intrahepatic arterial injection

After selective intrahepatic injection of ^{99m}Tc-labelled microspheres, over 90 per cent of injected microspheres were trapped within the liver (*Table 2*).

Discussion

Successful use of regional chemotherapy is based upon: the use of a drug with the appropriate pharmacokinetics (i.e. high systemic clearance and tumour extraction ratio) to which the tumour is intrinsically sensitive; correct catheter placement that allows infusion directly into the tumour; and use of a drug delivery system which allows repeated and long-term administration[2]. There have been a number of preliminary non-randomized studies which have evaluated intra-arterial cytotoxic infusions in the treatment of a variety of tumours including hepatic metastases, head and neck, renal, pelvic and primary and metastatic brain tumours. The results of these studies have been encouraging but require verification by larger, prospective randomized trials.

Recently attention has focused upon the potential use of microspheres to increase drug delivery and uptake. Laboratory studies demonstrated that after the intra-arterial administration of large diameter ethylcellulose microcapsules (approximately 225 μm diameter) containing 80 per cent by weight of biologically active mitomycin, there was a 60 per cent reduction in circulating systemic mitomycin compared with intra-arterial infusion of an identical dose of aqueous mitomycin[4]. Clinical responses have been reported in pelvic and oral tumours with microcapsules containing either mitomycin[5] or cisplatinum[6]. Ethylcellulose microcapsules are not biodegradable and permanently occlude the vessels in which they lodge. They have a dual therapeutic effect that arises from a combination of blood flow obstruction leading to tumour infarction and prolonged regional drug exposure.

An alternative is the concurrent intra-arterial injection of a suspension of starch microspheres within a drug solution which will temporarily decrease arterial blood flow and allow the drug to remain within the arterial capillary bed in high concentrations and, therefore, allow increased drug extraction by the tumour. It has been demonstrated that a dose of approximately 90×10^6 biodegradable starch microspheres (40 μm diameter) will totally occlude hepatic arterial flow in 25 per cent of patients[7]. By 30 min after injection the starch microspheres are completely lysed by serum amylase and subsequent doses can be administered without destroying access to the tumour's microcirculation. Yttrium-90 resin microspheres (55 μm diameter) have also been used to treat tumours by internal radiotherapy. The yttrium-90 microspheres have a short effective kill distance of 2–3 mm and deliver most of the dose over about 3 days[1].

In our study, after the intravenous administration of Adriamycin-loaded albumin microspheres, the microspheres

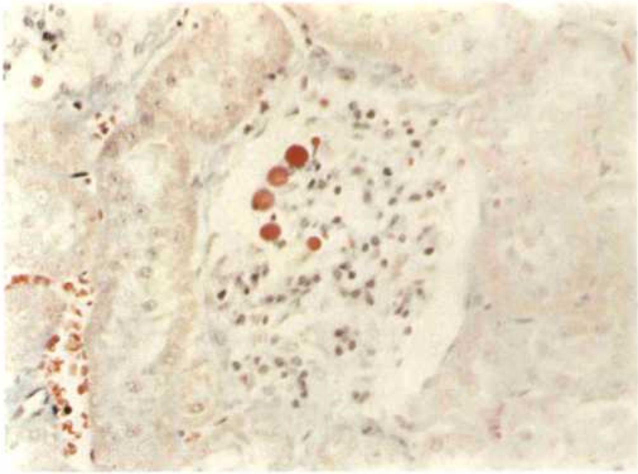

Figure 3 *Microspheres trapped in glomerulus*

Table 2 *Distribution of radiolabelled microspheres after selective intrahepatic arterial injection*

Liver	Kidney	Lung	Blood (per litre)
93±5	1·2±0·4	5·2±4·9	0·3±0·2

Results are expressed as a percentage of the total count and are presented as mean ± s.d. ($n = 4$)

were trapped in the pulmonary capillary bed and biodegradation occurred over the next 48 h. After selective right arterial injection of ^{99m}Tc-labelled microspheres, over 95 per cent of microspheres were trapped in the right kidney; in a similar manner, after intrahepatic arterial injection approximately 90 per cent of administered microspheres were trapped in the liver. Parallel studies in our laboratory have shown that when equivalent doses of Adriamycin (220 μg) were administered via the renal artery, either as free solution or in the form of Adriamycin-loaded microspheres, the serum Adriamycin levels after microsphere injection were significantly lower than those after the administration of free Adriamycin[8]. Similar results have been obtained using mitomycin-loaded biodegradable albumin microspheres[9].

The use of cytotoxic-loaded biodegradable microspheres, however, would not offer a substantial advance in the management of solid tumours unless it were possible to target these microspheres specifically towards the tumour tissue. Tumour blood vessels tend to be deficient in smooth muscle and have, therefore, an attenuated response to adrenergic stimuli. This property provides a potential method of diverting microspheres to the tumour, thereby further increasing the therapeutic ratio. Recent studies have shown that angiotensin II infusions produce a significant redistribution of organ blood flow, and can increase tumour blood flow by 100 per cent in patients with hepatic metastases[10].

In this study, over 90 per cent of albumin microspheres administered by selective intra-arterial injection were trapped in the target organ. The use of cytotoxic-loaded biodegradable microspheres, perhaps in conjunction with angiotensin II infusion, may have a potential role in the management of previously refractory solid tumours.

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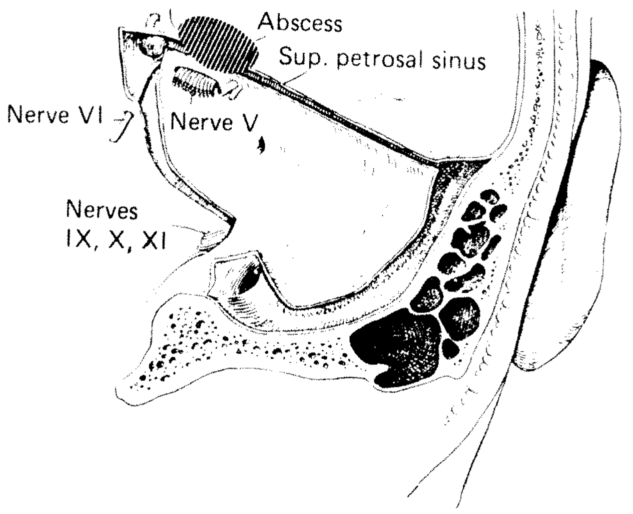

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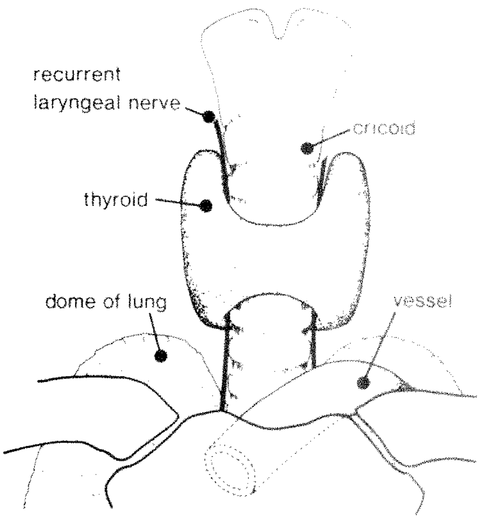

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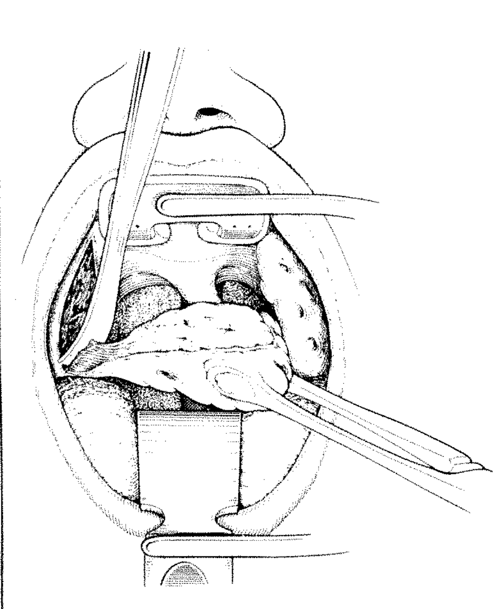

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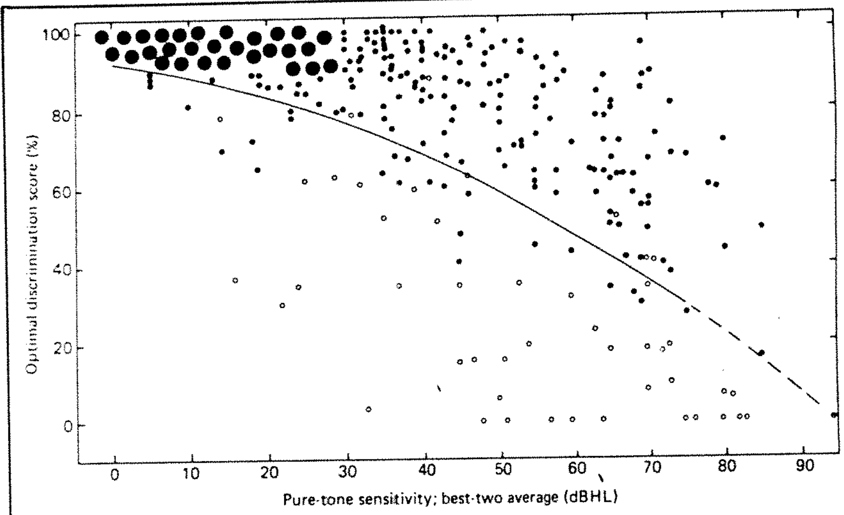

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Wound healing response in surgical patients: recent food intake is more important than nutritional status

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We have recently found that an impairment of the wound healing response (WHR) occurs in surgical patients with protein-energy malnutrition before there are any measurable changes in body fat and protein stores. The hypothesis of this study was that the patients' recent food intake is more important in determining the WHR than the patients' overall nutritional status. We have measured the recent food intake (by dietary recall), the WHR (by hydroxyproline accumulation in subcutaneous GORE-TEX implants), the pre-operative weight loss (per cent), and body fat and protein stores (by* in vivo *neutron activation analysis) in 83 patients awating a major elective gastrointestinal resection, and divided them into two groups: adequate recent food intake* (n = *59) and inadequate recent food intake* (n = *24). There was no significant difference between these two groups for age, sex, diagnosis, surgical procedure, weight loss (per cent), or the amount of body fat and protein stores but there was a significant difference in the WHR (1·81 ± 0·16 s.e.m.* versus *1·04 ± 0·22 s.e.m. nmol hydroxyproline/mg GORE-TEX*,* P < *0·005). These results show that pre-operative food intake has a greater influence over the wound healing response than absolute losses of protein and fat from body stores and they suggest that the maintenance of a normal food intake up until the time of surgery is of importance in preventing an impairment of the wound healing response.*

Keywords: Wound healing, food intake, nutritional status

We recently demonstrated an impairment of the wound healing response in surgical patients with protein-energy malnutrition, and suggested that this impairment occurred at an earlier stage of nutritional depletion than had been previously supposed[1]. Nutritional repletion of protein-depleted patients[2] and protein-depleted rats[3] does appear to be able to restore the wound healing response to normal within a short time, long before there is significant or measurable restoration of fat and protein stores. These studies suggest that a normal wound healing response may be more dependent on an adequate recent food intake than on substantial losses from fat and protein stores. This paper describes a recent study in which we examined the influence of food intake and losses of fat and protein from body stores on the wound healing response in surgical patients.

Patients and methods

Between March 1985 and August 1986, 83 patients awaiting some form of elective gastrointestinal resection agreed to enter this study. Patients receiving intravenous nutrition or steroids and those suffering from obstructive jaundice or diabetes mellitus were excluded. No patient had a haemoglobin concentration of less than 10·0 g/l before surgery. On the day before surgery a dietary and nutritional assessment was performed. The wound healing response was measured over a 7-day period beginning from the time of anaesthetic induction. The studies were carried out with the consent of the Auckland Hospital Human Ethical Committee.

The assessment of the wound healing response

Each patient's wound healing response was assessed at the time of surgery, by a technique modified from the method of Goodson and Hunt[3–5]. Immediately following induction of general anaesthesia, two 5 cm lengths of thin-walled 1 mm GORE-TEX (polytetrafluoroethylene, PTFE) tubing were inserted subcutaneously, 2 cm apart and in parallel, by a 14 gauge angiocatheter (Deseret) in the lateral aspect of the upper arm overlying the deltoid muscle. A length of polypropylene suture fastened to one end of the GORE-TEX tube was used to secure it to the skin with a Steri-Strip (3M Health Care Ltd) and this also enabled easy retrieval on the seventh day after wounding. The tissue collected in the interstices of the tubing (pore size of 90 μm) was analysed by spectrophotometry to quantify the amount of accumulated hydroxyproline[3,6]. The average of the two results was expressed as μmol hydroxyproline/mg dry GORE-TEX, and used as the measure of the wound healing response in that patient. In a study of 55 volunteers who had a normal food intake and nutritional status but who did not have an operation, the wound healing response was 1·53 ± 0·13 (mean ± s.e.m.) nmol hydroxyproline/mg GORE-TEX tubing (J. A. Windsor unpublished data). The mean difference between the pairs of GORE-TEX implants in the study of normal volunteers was 0·28 ± 0·91 s.d. The repeatability coefficient (standard deviation of the differences × 2)[7] for this method of assessing the wound healing response is 1·89

The assessment of recent food intake

The adequacy of the patients' food intake during the time of illness was carefully assessed on the day before surgery. On history, the most important factor noted was the meal size and any recent change in it. Patients who gave a definite history of a reduction of at least half of the normal amount of food eaten over a week before surgery were considered to have an inadequate recent food intake. No attempt was made to distinguish specific energy, protein or micronutrient deficiencies in the diet. Confirmation of a significant reduction in a patient's meal size was usually found by asking specific questions relating to any change in eating habit, the time course of any change, the amounts and types of food eaten, the frequency of intake and the presence of symptoms to substantiate any changes in intake (for instance, anorexia, abdominal pain and nausea). Validation of this approach to dietary assessment was made by a simple record method[8] in order to identify patients with an inadequate dietary intake. Therefore, 40 of the 83 patients were asked to record their total intake over a 24-h period for a representative day in the previous week. From the one-day recalled intakes, the energy (calories) and protein (grams of nitrogen) intake was calculated. An inadequate recent food intake was one in which the patient's intake was less than half of the recommended amounts[9] for energy and/or protein. There was good agreement

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Table 1 *Demographic data, surgical diagnoses and operative procedures in the patients before surgery*

	Patients with adequate food intake	Patients with inadequate food intake	*P*
n	59	24	
Age (years)	59·1±2·3*	65·4±1·6	n.s.
Sex (M:F)	31:28	11:13	n.s.
Height (cm)	165·4±1·1	163·5±1·7	n.s.
Surgical diagnoses			
Gastro-oesophageal			
Benign	6 (10·1)**	6 (25)	n.s.
Malignant	9 (15·2)	3 (12·5)	n.s.
Pancreatic			
Malignant	2 (3·4)	3 (12·5)	n.s.
Colorectal			
Benign	15 (25·4)	2 (8·3)	<0·05
Malignant	26 (44·2)	10 (41·7)	n.s.
Miscellaneous			
Benign	1 (1·7)	0 (0)	n.s.
Operative procedure			
Upper gastrointestinal			
Major	12 (20·4)	6 (25)	n.s.
Other	5 (8·5)	6 (25)	n.s.
Lower gastrointestinal			
Major	35 (59·3)	9 (37·5)	<0·05
Other	7 (11·8)	3 (12·5)	n.s.

* Mean±s.e.m.; ** number (%)

(93 per cent concurrence) between these two methods of dietary assessment in assigning patients to either the adequate or inadequate recent food intake group.

The assessment of nutritional status

The percentage weight loss was taken as the recalled well weight minus the current measured weight[10].

Body composition analysis. Prompt *in vivo* neutron activation analysis (IVNAA) and the tritiated water dilution technique were used to measure total body protein (TBP) and total body fat (TBF)[11]. The protein index[12], a measure of protein depletion, is the measured TBP divided by a predicted TBP. The predicted TBP was derived from linear regression equations using the age, height and sex of a local normal population who had had direct measurements of TBP. In the same way, a fat index was calculated from the measured and predicted TBF, and is used to measure the extent of body fat depletion.

Plasma protein concentration. Plasma albumin was measured by the bromocresol green method and plasma transferrin and prealbumin by laser nephelometry.

The assessment of postoperative course

After surgery each patient was carefully followed until discharge from hospital, with particular attention to the development of wound complications. Wound infection was defined as a discharge from the wound with a positive culture and wound dehiscence was that which required resuturing.

Statistical analysis. The unpaired Student's *t* test was used according to variance equivalence to determine the significant difference between the means of the single variables. In addition the Mann–Whitney *U* test was applied to the hydroxyproline measurements, and in all cases was in agreement with the parametric tests. Linear regression analysis was applied where appropriate. The postoperative complication rates were compared using the χ^2 test with Yates' correction unless expected values were less than 5 when Fisher's exact test was used.

Results

Wound healing response and nutritional status

No significant correlations were found between the amount of hydroxyproline that accumulated in the GORE-TEX tubes over the 7-day study period and any of the measurements of nutritional status: per cent weight loss ($r=0·14$), TBP ($r=-0·01$), TBF ($r=-0·04$), protein index ($r=-0·09$), fat index ($r=0·03$), albumin ($r=-0·08$), transferrin ($r=-0·19$), pre-albumin ($r=-0·07$). The wound healing response was, however, weakly correlated with age ($r=0·23$, $P<0·05$).

Wound healing response and recent food intake

The 83 patients were divided into two groups; those who had been eating normally up to the time of surgery ($n=59$) and those who had a reduction of at least half their normal food intake over the week before surgery ($n=24$). *Table 1* shows that there is no difference between the two categories of patients for age, height, sex, surgical diagnoses and operative procedures. *Table 2* shows that the wound healing response was significantly less ($P<0·005$) in the group with inadequate food intake, even though the two groups of patients could not be distinguished by percentage weight loss or body composition analysis. Exclusion of those patients who developed any type of infection during the period of analysis did not alter the degree of significant difference for the results of the wound healing response between the two categories of patient. Of the plasma proteins only transferrin was significantly reduced ($P<0·05$). Within the group of 24 patients who had an inadequate food intake before surgery, there was no clear relationship ($r=0·03$) between the wound healing response and the protein index, or any of the other indices of nutritional status.

Recent food intake and postoperative course

In this study no statistically valid ($\chi^2=2·16$) conclusions can be drawn from the data on wound complications because of the infrequency occurrence. Five complications (three infections, two dehiscences) occurred in the 24 patients who had not been eating adequately before surgery and eight complications (8 infections, no dehiscence) in the 59 patients who had been eating normally. The postoperative study in the two categories of patient was similar (17·4±13·6 days *versus* 16·1±7·4 s.e.m.).

Discussion

Our results show that pre-operative food intake has a greater influence over the wound healing response than absolute losses of protein and fat from body stores. They suggest that the maintenance of a normal food intake up until the time of surgery is of importance in preventing an impairment of the wound healing response.

These results help to explain our previous findings[2,3] in which an improvement in the wound healing response, but not

Table 2 *The measurement of the wound healing response, percentage weight loss, body composition, and plasma proteins in the 2 groups of patients*

	Patients with adequate food intake $n=59$	Patients with inadequate food intake $n=24$	*P*
Wound healing response			
Hydroxyproline (nmol/mg GORE-TEX)	1·81±0·16*	1·04±0·22	<0·005
Nutritional status			
Body weight (kg)	63·9±1·9	59·7±2·3	n.s.
Weight loss (%)	9·01±1·14	11·05±1·67	n.s.
Total body protein (kg)	8·25±0·42	7·04±0·50	n.s.
Protein index	0·82±0·03	0·74±0·03	n.s.
Total body fat (kg)	15·48±1·04	16·04±1·78	n.s.
Fat index	1·05±0·08	0·98±0·10	n.s.
Plasma proteins			
Albumin (g/l)	39·5±0·63	38·2±1·07	n.s.
Transferrin (mg/dl)	246·2±8·5	214·7±14·5	<0·05
Pre-albumin (mg/dl)	19·6±1·1	17·5±1·6	n.s.

* Mean±s.e.m.

nutritional status, was detected over a 1–2-week period, in both rats (that were protein starved and then refed) and in patients (that were given intravenous nutrition). The new information that has been derived from this study is that an adequate recent food intake is able to maintain the wound healing response regardless of the patients' nutritional status. An inadequate food intake over the week before surgery is able to impair the wound healing response to a similar extent to that found in our earlier studies[1,2]. This brings into question the long-held belief that the loss of body protein stores is associated with a delay in wound healing[13,14].

The findings of this study are supported by a recent paper[5] which showed that an acute pre-operative illness has an adverse effect on postoperative wound healing. A reduction of 20 per cent in hydroxyproline accumulation was related to the duration of the acute pre-operative illness. This impairment in postoperative wound healing might be explained by an inadequate food intake accompanying the acute pre-operative illness, although this was not assessed.

The influence of recent food intake on the wound healing response might well relate to its effect on the patients' labile protein reserves[15–17]. These reserves are maintained by an adequate protein intake and might be seen to provide a biological advantage in the face of depleted total body reserves for a range of body functions, including wound healing and skeletal muscle function[18–20].

Waterlow *et al.*[21] investigated the influence of eating on whole body protein turnover using isotopic techniques. They showed that a fall in the rate of protein synthesis occurs within 2 days of the change to a protein-free diet in normal subjects. There are also alterations in plasma amino acids and plasma proteins with short-term starvation. These fundamental responses to starvation may explain the type of improvements we have noted in the present study. It is known, for instance, that the sulphur-containing amino acids, such as methionine and cystine, are important in the wound healing process and that plasma protein levels are associated with wound healing. It has been demonstrated that low total plasma protein concentration is associated with a higher incidence of wound breakdown[22,23].

It has been argued[24] that the amount of collagen present in a healing wound is not the critical factor in the development of wound strength, but that it is due to the cross-linking within the collagen fibrils. In response to this, we contend that the measurement of hydroxyproline concentration in a subcutaneous implant is not used in this study to determine ultimate wound strength, but rather to measure the wound healing response in the broadest sense. As such, this technique has been shown to monitor and detect[1] the very biological events that protein depletion has been thought to affect adversely[25]. These include the acute inflammatory response, cellular invasion, macrophage stimulation, fibroplasia and collagen production. All these processes play a vital role in host defence and the measurement of an impairment or an improvement in them can only be of importance to the patients' postoperative course.

It is clear that the wide inter- and intra-patient variation in the wound healing response, as previously found[1,3] using this subcutaneous implant technique, did not prevent the detection of significant differences between groups of patients with varying food intakes and nutritional status.

In modern surgical practice it is not unknown for patients to have a period of reduced food intake for several days before a major surgical procedure. The illness itself, the necessity for radiological investigations and the inattention given to dietary advice may all contribute. We have shown recently that pre-operative intravenous nutrition over the period has a beneficial effect on the wound healing response. Further work is now needed to see if simpler and less expensive measures will achieve the same effect.

Acknowledgements

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Prediction of choledocholithiasis using a pocket microcomputer

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A computerized method, using a small pocket computer, has been used to predict the presence of choledocholithiasis in a prospective series of 239 patients undergoing cholecystectomy. From an initial data base of 424 patients 36 factors were evaluated and the most important 2 of these were determined by multivariate analysis for use in the prospective analysis. Satisfactory operative cholangiograms were a prerequisite to evaluation of the statistical method and were obtained in 90·4 per cent of cases. Using the computerized method a common bile duct stone would have been overlooked in only 1 patient but 17 unnecessary explorations would have been carried out. The overall accuracy of the computerized method was 92·5 per cent. When the method was applied to a further study of 97 patients from a separate centre the overall accuracy was 85·6 per cent. If the method was used to aid selective use of operative cholangiography, cholangiograms would be performed in 20 per cent and stones would be overlooked in less than 1 per cent.

Keywords: Gallstones, choledocholithiasis, operative cholangiography, bile duct, microcomputer

Cholecystectomy is the most common abdominal operation performed in westernized countries; more than half a million are carried out annually in the USA. Approximately 15 per cent of patients have choledocholithiasis[1] and the retained, or overlooked, common bile duct stone remains a serious clinical problem despite the availability of operative and completion cholangiography, the choledochoscope and operative ultrasonography[2,3]. Conversely, unnecessary exploration of the common bile duct increases the operative mortality and morbidity.

Operative cholangiography is not always employed routinely at cholecystectomy and was used in only 25 per cent of patients in an early study of its selective use from Ohio[4]. A recent report addressed the use of either selective or routine intra-operative cholangiography and claimed both lower costs and lower mortality for a policy of selective use[5]. The obvious benefits of detecting more stones were, in this study, counterbalanced by increased costs, morbidity and false positive cholangiograms leading to unnecessary exploration of the common bile duct.

The aim of this study was to assess the feasibility of using a simple portable computerized method of predicting the presence of common bile duct stones and to compare this with operative cholangiography.

Patients and methods

A consecutive series of 663 patients undergoing surgery for cholelithiasis has been studied. An initial data base was compiled from the first 424 of these patients[5]. A proforma of 36 factors (*Table 1*) was used and analysed by univariate analysis.

A second and sequential prospective study was then carried out on a further 239 patients also undergoing cholecystectomy. All of the patients used in the study had a satisfactory operative cholangiogram. Cholangiography was performed with the patient supine by injecting 3, 8 and 16 ml of 25 per cent Hypaque, taking three films accordingly. Every patient who underwent exploration of the common bile duct had a completion, on-table, cholangiogram performed and a T-tube cholangiogram on approximately the eighth postoperative day. An additional 23 patients (9·6 per cent) have been excluded because of a technically inadequate cholangiogram. A retained common bile duct stone was defined as one identified on T-tube cholangiography or detected within 1 year of cholecystectomy.

A Sharp pocket microcomputer was programmed to use two variables identified as being of significance from the initial data base. The information for these variables was available at the time of operation before the duct was explored. The computer printout gave the probability of the presence of stones in the common bile duct on a percentage basis.

A third study was performed on 97 patients whose data were collected prospectively by another surgeon (A.A.G.) in a separate centre. These data were surveyed using the total data base of 663 patients to determine the accuracy of prediction of the presence of choledocholithiasis in an independent centre.

Results

The initial data base, when recalculated by an improved method of discriminant analysis, indicated an accuracy of prediction of choledocholithiasis in 88·4 per cent. Stones in the common bile duct would have been overlooked in 3 per cent and 8·5 per cent would have had unnecessary and therefore negative

Table 1 *Variables assessed in the initial data base*

- Age
- Sex
- Length of history
- Presentation
  - Biliary dyspepsia
  - Acute cholecystitis
  - Chronic cholecystitis
  - Biliary colic
  - Pancreatitis
  - Back pain
  - Jaundice
  - Cholangitis
- Oral cholecystogram or intravenous cholangiogram
  - Number of stones
  - Wall thickened
  - Non-function
- Gallbladder at operation
- Number of stones
  - Wall thickened
  - Empyema (mucocele)
  - Mucosal disease
- Common bile duct
  - Normal sized
  - Dilated ($\geqslant 10$ mm)
  - Stones palpable
- Pancreas
  - Normal
  - Abnormal

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Table 2 *Findings on operative cholangiography relative to the recovery of stones following choledochotomy*

Operative cholangiogram finding	Stones recovered	No stones recovered
Stones	31	8
No stones	0	201

Sensitivity 100%
Specificity 96·2%
Efficiency 96·7%

Failed examinations 23 (9·6%)

Table 3 *Computer prediction relative to recovery of stones at choledochotomy*

Computer prediction	Stones recovered	No stones recovered
Stones	30	17
No stones	1	191

Sensitivity 96·8%
Specificity 91·8%
Efficiency 92·5%

explorations[6]. The factors found to be of predictive significance, in order of importance were bile duct diameter (V_1) and the presence of more than ten gallbladder calculi (V_2). The equation obtained by discriminant analysis was: Score $= 3{\cdot}09V_1 + 0{\cdot}39V_2 - 6{\cdot}12$. A negative value indicated the presence of a duct stone; conversely the positive value indicated that no stone was present.

Of the 239 patients, 31 had a stone in the common bile duct (13·0 per cent). The operative cholangiographic data is shown in *Table 2* with an overall accuracy for determining the presence of common bile duct stones of 96·7 per cent. Detracting from this figure is the additional 9·6 per cent of cases who had to be excluded because of either a failed or inadequate cholangiogram. No common bile duct stones were missed when the technique of operative cholangiography was totally satisfactory. However, in eight patients the presence of stones was falsely predicted and all of these underwent unproductive exploration of the common bile duct.

The accuracy of computer diagnosis in the prediction of common bile duct stones is shown in *Table 3*. In only one patient would a common bile duct stone have been overlooked. This patient had a normal calibre duct with no history of jaundice or pancreatitis. Seventeen patients would have had unnecessary explorations on the basis of computer diagnosis but the overall accuracy was 92·5 per cent, only 4 per cent less than that achieved with routine and satisfactory cholangiography. Computer diagnosis was available in all patients as opposed to 90·4 per cent of the patients in whom cholangiography was performed.

The prospectively gathered data from 97 patients in another centre is shown in *Table 4*. In these patients the computer prediction did not overlook the presence of any choledochal stones, but stones were predicted in 14 patients in whom none was actually present, reducing the specificity to 82·1 per cent and the overall accuracy to 85·6 per cent.

If operative cholangiography had been used selectively in only those patients in whom the computer predicted the presence of a stone, in the first study reported here 47 cholangiograms would have been performed in 239 cases (19·7 per cent) and in the second study 19 in 97 cases (19·6 per cent).

Discussion

A majority of surgeons do not routinely use operative cholangiography and there may be an argument for employing this procedure only in selected cases. In our prospective study cholangiography failed to produce adequate films in 10 per cent of patients. Technically unsatisfactory films may be obtained because of failure to fill the duct system, overfilling of the ducts resulting in the complete immersion of stones, the introduction of air bubbles, absent duodenal filling, and extravasation of contrast material[7,8]. Other potential disadvantages of cholangiography are possible contamination of the operative field, biliary leakage following needle puncture, small duct injury, extended operating time and the irradiation hazard[9]. Interest is increasing in the more selective use of operative cholangiography. One study[10] reported an incidence of only 0·03 per cent retained common bile duct stones following cholecystectomy and the selective use of operative cholangiography using five simple criteria. Furthermore, using a similar method, Gerber and Apt[11] performed operative cholangiography in only 62 of 500 patients undergoing cholecystectomy and only one of the patients in this study required reoperation for a retained stone. Employing operative cholangiography routinely resulted in an incidence of false positive results and the presence of unsuspected stones in 3·1 and 2·5 per cent respectively of 2580 cholangiograms[12]. It may be that with simple statistical methods, the sensitivity and specificity achieved by the selective use of cholangiography in the detection of choledocholithiasis can be increased.

Increasing experience may change the statistical equation obtained from the multivariate analysis and may change the order of variables or the variables themselves making up the discriminant function, as was the case when our data base expanded from 424 to 663 cases (*Table 5*). The common bile duct diameter remains by far the most important discriminant in predicting the presence of bile duct stones. It is possible that the value of this discriminant could be further increased by estimating the degree of dilatation rather than simply whether or not dilatation was present, and loading the equation accordingly[13]. Interestingly the third most important factor was the male sex, men being significantly more likely to have bile duct stones than women. This may relate to the larger duct system in men which would be expected to be more conducive to the passage of gallstones, or to the anatomy of the sphincter of Oddi[14–16]. The other variables, namely presence of biliary colic and number of gallbladder stones, are perhaps predictable, although much of the information relating to the presence of stones in the common bile duct is conveyed in the first variable, duct dilatation.

The prospective study of our own patients and that of the separate group from another hospital both showed that only one stone was overlooked (in 336 patients) using the

Table 4 *Computer prediction relative to recovery of stones at choledochotomy in 97 patients studied prospectively at an independent centre*

Computer prediction	Stones recovered	No stones recovered
Stones	19	14
No stones	0	64

Sensitivity 100%
Specificity 82·1%
Efficiency 85·6%

Table 5 *Discriminant equation obtained from 663 cases*

Score $= 6{\cdot}58 - 3{\cdot}19V_1 - 0{\cdot}40V_2 - 0{\cdot}33V_3 + 0{\cdot}25V_4$

V_1	Bile duct diameter 10 mm	(Yes = 1, No = 2)
V_2	More than 10 gallbladder calculi	(Yes = 1, No = 2)
V_3	Sex	(Male = 1, Female = 2)
V_4	History of biliary colic	(Yes = 1, No = 2)

computerized method. Unnecessary explorations of the common bile duct would have been performed in 31 patients but this figure must be kept in perspective. It is often not appreciated that negative exploration of the common bile duct is a common and undesirable event, the reported range of negative exploration ranging from almost zero up to 50 per cent[17–21]. Using computer prediction the incidence would have been 9 per cent. While negative explorations carried no mortality in our series, they definitely led to increased morbidity and prolonged hospitalization.

The variables selected by multivariate analysis can be available to the surgeon pre-operatively with the routine use of good ultrasonography to estimate the number of gallbladder stones and the common bile duct diameter, although ultrasound is unreliable in visualizing common bile duct stones. Thus the system of computer analysis could predict pre-operatively whether or not the surgeon needs to explore the common bile duct. Should doubt exist then operative cholangiography may be employed as the final arbiter before duct exploration. The use of this system of microcomputer analysis allows a truly selective policy of cholangiography to be employed to maximize the accuracy of stone detection. If operative cholangiography was used selectively in those patients who had a stone predicted by computer, cholecystograms would be performed in only 20 per cent and stones would be overlooked in 0·3 per cent of cases.

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Urgent and early cholecystectomy for acute gallbladder disease

A retrospective study of 645 cholecystectomies performed in a surgical unit over a 10-year period is presented, of which 236 were carried out during an acute admission. Of these 236 cholecystectomies, 195 were performed for acute cholecystitis and 41 for acute gallstone pancreatitis. In the acute cholecystitis group the proportion of patients over 70 years of age was significantly higher (35 per cent) than the corresponding elective group (10·3 per cent). Of those patients presenting with complications (empyema, gangrene, perforation, and biliary peritonitis) 51 per cent were over the age of 70 years. The most valuable investigation in the diagnosis of acute cholecystitis was ultrasound carried out within the first 48 h, with positive results in 83 per cent of those examined. The mortality for elective cholecystectomy was 0·5 per cent rising to 4·7 per cent in the urgent/early cholecystectomy group. The mean age of the 11 patients who died was 76 years, 8 of these patients being over the age of 70 years. The mortality in the subgroup of patients over 70 years was 10 per cent rising to 20 per cent in the over-80 age group. There were no deaths in the acute gallstone pancreatitis group. We conclude that emergency or early cholecystectomy is a safe procedure in patients under 70 years of age. However, patients over 70 years present with more serious complications of acute gallbladder disease which necessitate urgent surgery. We therefore recommend early cholecystectomy in patients over 70 years despite the high attendant mortality.

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Keywords: Acute cholecystitis, diagnosis, urgent/early cholecystectomy

The majority of general surgeons still treat acute cholecystitis conservatively with intravenous fluids and analgesia, usually in conjunction with antibiotics. Delayed cholecystectomy is carried out during a second admission after the acute attack has settled down. A recent study from Sweden[1] showed that in 81 per cent of surgical departments delayed operation is still the most commonly used procedure. During the last 15 years there have been many controversial reports recommending early surgery as the treatment of choice and Ganey *et al.*[2] support this approach with their remarkably low overall mortality of 0·5 per cent. However, in a recent paper, Alinder *et al.*[3] make the comment that 'most surgeons still look on an acute cholecystectomy as a hazardous operation and it is still mostly performed only if the patient's condition is deteriorating during the first 24 to 48 h after admission'. Our main object was to clarify from our own experience this controversial topic of early *versus* delayed cholecystectomy.

Patients and methods

Over the 10-year period 1975–84 a total of 645 cholecystectomies have been performed on patients under the care of one consultant (N.V.A.). Of these, 236 (37 per cent) were undertaken during the first acute admission. The case records of all patients were retrieved and a standard pro forma completed. Details of the patients' age and sex are included in *Table 1*. All patients having urgent (within 48 h) or early (during the same admission) cholecystectomy presented with the symptoms and signs suggestive of acute gallbladder disease (195 patients) or acute pancreatitis (41 patients). Forty-one patients with obvious localized or generalized peritonitis on presentation had few investigations before urgent surgery. No patients were included who had a laparotomy with a pre-operative diagnosis of biliary tract disease, but were found to have some other pathology at operation which was the cause of their illness Where the condition of the patient allowed, the clinical diagnosis of acute gallbladder disease was confirmed with laboratory investigations and one of several imaging techniques. Over the 10-year period we have come to rely increasingly on ultrasound performed within the first 48 h. No patient with a diagnosis of acute cholecystitis was treated conservatively because of poor general condition due to such problems as cardiac or respiratory illness.

In all but the urgent cases, patients underwent surgery on the next available elective list (early cholecystectomy) Cholecystectomy was performed through a paramedian incision using one of two standard techniques (fundus first, 76 per cent; cystic duct first, 24 per cent). Operations were carried out by either a consultant or senior registrar in all instances. The former used the 'fundus first' technique routinely in all cases. The 'cystic duct first' technique was employed by senior registrars only until they were trained to use the 'fundus first' technique, especially in acute cholecystitis.

The pathological state of the gallbladder was classified as 'uncomplicated' where the features were of acute cholecystitis alone, or 'complicated' when an empyema, mucocele, gangrenous gallbladder or frank perforation was present.

Table 1 *Details of patients undergoing elective and urgent/early cholecystectomy in the period 1975–84*

Cholecystectomy	Mean age (years)	Sex	No. of patients	Percentage
Elective	51·3	Male	106	26
		Female	303	74
Urgent/early	58·5	Male	74	31
		Female	162	69

Age range (years)	Urgent/early (percentage of cases)	Elective (percentage of cases)
10–19	0·4	0·7
20–29	9·0	8·9
30–39	10·7	11·6
40–49	12·0	19·8
50–59	16·3	26·7
60–69	16·3	22·0
70–89	35·1	10·3

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Table 2 *Bacteriology of bile (acute cholecystitis), available in 114 cases*

Sterile in 62 cases (54%)		
Infected cases		
Single organisms	42	
Two organisms	9	
Three organisms	1	
Total of 62 isolates in 52 patients		
Escherichia coli	31	60%
Klebsiella	13	25%
Staphylococcus aureus	4	8%
Streptococcus faecalis	3	6%
Clostridium welchii	3	6%
Streptococcus viridans	3	6%
Staphylococcus albus	2	4%
Bacteroides	1	2%
Salmonella	1	2%
Proteus	1	2%

No consistent antibiotic policy was adopted throughout the series although it has been the routine in recent years to obtain a specimen of gallbladder bile for culture Patients identified as high-risk, including the elderly, jaundiced, and those with proven common duct stones, were given a parenteral cephalosporin for 48 h (starting immediately before operation).

Further information obtained from the notes included time to surgery, length of postoperative stay and full details of those patients who died in this series. Mortality was defined as death for any reason during the same admission or within 30 days of surgery Statistical analyses of differences within patient groups were made by the χ^2 test.

Results

Table 1 shows a predominance of female patients. When comparing the early with elective cholecystectomy groups there was no significant difference either in proportion of males:females or in the mean age. It should be noted that the proportion of patients' over 70 years of age in the early group was significantly higher than that in the elective patients (35·1 per cent *versus* 10·3 per cent, $P<0\cdot001$).

In the urgent/early group the serum alkaline phosphatase and bilirubin were elevated in 77 per cent and 84 per cent of patients respectively, where measured. By comparison the alkaline phosphatase was elevated in the elective group in only 26 per cent of cases. In the radiological investigations within the urgent/early cholecystectomy group for acute cholecystitis, plain abdominal radiographs were obtained in 180 of the 195 patients; of these, only 17 per cent showed gallstones and contributed to the diagnosis. Ultrasound examination of the gallbladder was of increasing importance throughout this series and although performed in only 43 per cent of cases it revealed positive findings in 83 per cent of them.

In both the urgent/early and elective groups the 'fundus first' technique of cholecystectomy predominated (76 per cent acute, 66 per cent elective) as the decision to adopt a particular method depended more on the individual operating surgeon. Operative cholangiography was performed in the elective group in 87 patients, and in the urgent/early group in 21 patients. On-table cholangiograms were not routinely used in this series of cholecystectomies. There was no instance of damage to the common bile duct in this series. There was no difference in the proportion of patients undergoing exploration of the common duct in the urgent/early group (25 per cent) *versus* the elective group (22 per cent). Of the 195 patients undergoing urgent/early cholecystectomy for acute gallbladder disease, 139 were found to have uncomplicated acute cholecystitis. The remaining 56 (29 per cent) had either a mucocele ($n=20$) empyema ($n=17$), or gangrene or perforation ($n=19$). More than one-half of the complicated cases (51 per cent) concerned patients over 70 years of age, although this group accounted for only 35 per cent of patients undergoing urgent or early operation.

The results of bacteriological examination of the bile are shown in *Table 2*. Bile was obtained from the excised gallbladder and sent immediately to the laboratory. At night, swabs were placed in Stewart's medium and sent to the laboratory the following morning. It is to be noted that there was no growth in over one-half of the cases where bile was examined.

The number of days between operation and discharge from hospital was 12·8 in the elective cholecystectomy patients and 13·6 in the urgent/early group.

The mortality for elective cholecystectomy over this 10-year period was 0·5 per cent rising to 4·7 per cent in the urgent/early cholecystectomy group. Details of the patients who died in the urgent/early group and their causes of death are shown in *Table 3*. The mean age of 11 patients who died was 76 years, 8 of these patients being over the age of 70. The mortality in the subgroup of patients over 70 years was 10 per cent rising to 20 per cent in the over-80 age group.

Discussion

One of the main arguments against early surgery in acute cholecystitis centres on the difficulty of making an accurate diagnosis during the attack. It is well known that of those patients admitted urgently to hospital with a clinical diagnosis of acute cholecystitis, between 8 per cent and 33 per cent prove not to have gallbladder disease on investigation[4]. In a recent prospective study[5], 25 of 100 patients were found to have a different diagnosis on investigation, and in 11 patients a definite diagnosis could not be established. During the last decade, diagnosis has become easier and more accurate with the advent of ultrasonic scanning[6,7]. It is now our practice to rely on ultrasound, which in our hands was positive in 83 per cent of patients subsequently found to have gallstones at operation. Ultrasound can demonstrate the presence of gallstones and, more importantly, features such as a thickened gallbladder wall or a localized abscess. Although others believe that technetium HIDA scintigraphy is more specific[8], improvements in ultrasound techniques, together with the expense of HIDA scintigraphy, lead us to believe that ultrasound remains the method of choice. The third specific investigation used is contrast tomography[4]; we have no experience of this technique, which is said to be the only procedure to give direct information about the presence of acute cholecystitis. A recent report[9] described infusion cholecystography as the initial investigation in acute biliary tract disease. The study confirmed its usefulness and reliability, especially if employed in conjunction with ultrasonography, achieving a diagnostic rate similar to that afforded by HIDA scintigraphy.

Where the ultrasonic findings were inconclusive, deranged liver function tests provided supportive evidence in favour of a diagnosis of acute cholecystitis. The serum alkaline phosphatase was raised in 76 per cent and the serum bilirubin in 84 per cent of our patients in the acute group.

Although the problem of diagnosis has been claimed to be

Table 3 *Mortality* in the series of urgent and early cholecystectomies*

Patient no.	Age† (years)	Sex	Cause of death	Days after operation
1	72	F	Cardiorespiratory failure	90
2	75	M	Myocardial infarction	2
3	80	M	Bronchopneumonia	5
4	83	M	Respiratory and renal failure	12
5	83	M	Respiratory failure	30
6	69	M	Bronchopneumonia	20
7	79	M	Myocardial infarction	8
8	83	F	Congestive heart failure	60
9	85	F	Bronchopneumonia	25
10	58	M	Myocardial infarction	12
11	69	F	Septicaemia	7

* Overall mortality rate=4·7% (11/236)
† Mean age=76 years

the main reason for late surgery, other reasons such as technical difficulty in performing cholecystectomy, increased blood loss, operative complications, increased sepsis and mortality have been offered by those who argue against early operation. However, in acute cholecystitis the gallbladder wall is thickened and oedematous, and the oedema is responsible for most of the wall thickening. Although the serous surface is congested and covered with a fibrinous exudate, this is not purulent, polymorphs and bacteria are relatively few, and the inflammatory exudate is more marked in the outer layers of the wall. It is this outer wall oedema that provides a plane of cleavage between the liver and the gallbladder, facilitating enucleation and making cholecystectomy less difficult in the acute stage[10] rather than when this phase has settled down with the formation of postinfective fibrous tissue. Lahtinen *et al.*[11] also take the view that it is easier to perform, and that the operation time is significantly shorter.

Bile acids and salts are known to have an inhibitory effect on the growth of organisms, and sometimes in an empyema with minimal bacterial content, the creamy contents may not be frank pus but an emulsion of cholesterol crystals and calcium carbonate. It was worthy of note that the bile was sterile in 54 per cent of those cases where bacteriology was carried out. In this study the organisms that we have encountered are the same as those reported by others and include *Escherichia coli*, non-haemolytic streptococci, *Klebsiella* and occasionally *Clostridium welchii*.

We advocate a 'fundus first' removal, especially for a mucocoele or empyema, for many reasons. When the gallbladder is distended with acute inflammation of the wall, associated adhesions to the stomach and colon and often a localized abscess, it can be difficult to isolate the cystic duct–common bile duct junction, and cystic artery as a preliminary procedure. We firmly believe that on occasions a fundus first cholecystectomy can be the only safe way to remove an acutely inflamed gallbladder in order to obviate the risk of damage to the common hepatic/bile ducts. Even those advocates of the 'cystic duct first' technique may, under difficult operative circumstances, have to abandon this approach and resort to the 'fundus first' technique. Adherence to these surgical principles in 'fundus first' cholecystectomy is justified by the fact that no damage to the hepatic or common bile duct was encountered in our series.

Complications of acute gallbladder disease include gangrene, perforation and the formation of a localized abscess and occasionally biliary peritonitis. Although the risk of perforation is slight, it does occur in 3–12 per cent of patients and is especially problematic in the elderly. In this series 35 per cent of the acute group were over 70 years of age and it is within this elderly group that the majority of complicated cases occurred. Thus, early operation in the first few days can deal with these complications, especially in the elderly[12,13]. Patients over 70 years old are more liable to be admitted as emergencies with a more likely chance of perforation of the gallbladder and therefore require urgent/early surgery[14]. Protagonists of delayed surgery have suggested that mortality and morbidity is increased with early surgery but trials have shown that this is the same in both the early and delayed groups. Norrby *et al.*[15], in a prospective randomized trial, showed that there was no difference in the frequency of intra- and postoperative complications, and the incidence of bacterial complications was markedly lower in the early group although a moderate but significantly greater intra-operative blood loss was reported.

The number of days between operation and discharge in our series was approximately the same (elective 12·8, urgent/early 13·6). This agrees with the work of others[3,16] who claim that there is no increase in the number of days from operation to discharge in the early group compared with the delayed group and the former therefore is more cost effective. Some authors have shown that between 22 per cent and 27 per cent of patients who are sent home to await delayed surgery will be re-admitted with a further attack during the waiting period[11,15].

One of the few prospective randomized trials using the 'fundus first' technique in both groups, reports 83 early cholecystectomies (within 7 days) and 82 delayed cases[17]. There were no differences in the incidence of technical difficulty measured by operative complications and duration time of operation between the two groups. There was no statistical difference in postoperative complications between the two groups, although wound complications were slightly more common in the early group, and in the delayed group 13 per cent required emergency surgery. One death occurred in the delayed group but none in the early group.

The mortality for elective cholecystectomy (409 patients) was 0·5 per cent and for acute cholecystitis and acute pancreatitis (236 patients) 4·7 per cent overall, rising to 10 per cent in the 70+ age group and 20 per cent in those patients over 80 years. This compares favourably with the mortality of 19 per cent reported by Houghton *et al.*[13]. There was no surgical mortality in the acute gallstone pancreatitis group (41 patients). We conclude that, in acute cholecystitis, urgent or early cholecystectomy is a very safe procedure in patients under 70 years of age. In our experience patients over 70 years present with more serious complications of acute gallbladder disease, which require urgent or early surgery. The traditional conservative management of these patients may prove fatal and, despite cardiorespiratory disease, obesity and other attendant diseases of the aged, we recommend early cholecystectomy despite the high mortality.

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Non-invasive treatment for retained common bile duct stones in patients with T tube in situ: saline washout after intravenous ceruletide

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The combination of ceruletide-induced relaxation of the sphincter of Oddi plus flushing with saline has recently been proposed as a novel procedure for the treatment of residual common bile duct (CBD) stones. In this study we have administered intravenous ceruletide (2 ng kg^{-1} body weight min^{-1} for 1 h) plus intraductal saline (800–3000 ml, infused at a rate that kept biliary pressure below 30 cmH$_2$O) to a group of 14 patients. The treatment induced the passage of residual stones in 11 subjects (79 per cent) with complete clearance in 7 (50 per cent). The majority of the cleared concretions (11/15) had a diameter <10 mm. No severe side-effects were recorded during the treatment. Four of the seven subjects who exhibited incomplete CBD clearance underwent a short cycle of mono-octanoin administration in order to reduce the size of residual radiolucent stones. This course of treatment was followed by another attempt with intravenous ceruletide and saline washout which gave a successful response in an additional three cases. These data indicate that the combination of ceruletide and flushing is a safe and inexpensive method for treatment of residual stones. The procedure is feasible for both radiolucent and radio-opaque stones and is mainly eligible for small concretions of diameter <10 mm. Larger (>10 mm) radiolucent stones may be partially dissolved with mono-octanoin and then eliminated by the washout technique.

Keywords: Ceruletide, choledocholithiasis, mono-octanoin, saline washout, T tube

Retained common bile duct (CBD) stones are still a major therapeutic problem and are found in about 10 per cent of patients who have undergone surgical exploration of the CBD[1].

As CBD stones over 5 mm in diameter are unlikely to disappear spontaneously[2] and surgical re-exploration of the biliary tract is associated with a high risk of mortality and morbidity[3], many efforts have been devoted to develop non-surgical therapeutic options[4]. When a T tube is *in situ* and the concretion lies below the biliary drainage, flushing with saline[5] or dissolution with litholytic agents[6] has been attempted, yielding variable success rates (20–70 per cent of cases). In this context, Cuschieri[7,8] has recently suggested that the flushing technique can be improved by combining intraductal instillation of saline and intravenous administration of ceruletide, a synthetic analogue of cerulein, which allows relaxation of the sphincter of Oddi[9]. According to this author[7,8], the results of this novel procedure are superior to those obtained by mono-octanoin and indicate that this simple and inexpensive method of treatment should be tried before more invasive techniques.

The purpose of this report is to describe our experience with this method in 14 patients with retained biliary stones. In addition, we suggest a possible use of the procedure in association with mono-octanoin.

Patients and methods

Between May 1985 and December 1986, 14 patients (3 men, 11 women) with retained stones were referred to our university unit from other hospitals. *Table 1* lists the demographic and clinical characteristics of these patients, who had open access to the biliary tree through a T tube (12–16 Fr) placed at the time of the previous cholecystectomy and exploration of the CBD.

All subjects were asymptomatic and had their T tube clamped off for 3 weeks or more to restore bile flow without the stones passing spontaneously into the gut through the intact papilla. After an overnight fast, the patients received ceruletide IV (Takus, Farmitalia, Milan, Italy) at the dose of 2 ng kg^{-1} body weight min^{-1} for 1 h plus intraductal sterile saline (800–3000 ml). During the infusion an online manometer was used to monitor pressure constantly within the biliary system. The manometer was broken off at the 30 cm mark to prevent excessive pressure in the biliary system. Each patient reported the development of any side-effect during the procedure. In some cases the flushing treatment was repeated up to a maximum of four times allowing an interval of at least 24 h between one treatment and the next.

Blood laboratory tests, including routine analysis (complete blood counts, blood urea nitrogen, electrolytes) and hepatopancreatic function tests (serum bilirubin, transaminases, alkaline phosphatase, serum and urine amylase) as well as bile cultures[10] were checked before and after any washout with saline. The criterion for success was a post-washout choledochogram showing the disappearance of the stone(s).

The subjects with radiolucent CBD stones who did not respond to flushing with saline plus ceruletide underwent a cycle of therapy with mono-octanoin (Capmul 8210, Stokely Van Camp Co., Indianapolis, Indiana). To obtain preliminary information on the capability of mono-octanoin to dissolve the residual concretions, one retrieved stone from the previous cholecystectomy was placed in a test tube with 20 ml mono-octanoin. The test tube was sealed and maintained at 37°C. The stones were carefully weighed before the start of the experiment and after 4 days' incubation. The procedure is worth doing as matched gallstones from the same gallbladder have similar composition and dissolution rates in cholesterol solvents[11]. The modalities of mono-octanoin administration were similar to those previously described[12]. Serial cholangiograms were performed to evaluate the effectiveness of the litholytic therapy. The data are expressed as the mean ± s.e.m.

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Table 1 *Demographic characteristics of patients with retained stones and details of the first treatment with intraductal instillation of saline and IV infusion of ceruletide*

Case No.	Age (years)	Sex	No. of stones divided according to size before treatment <10 mm	>10 mm	Type of stones*	Interval between surgery and residual stone treatment (weeks)	Saline infused (ml)	No. of stones divided according to size after treatment <10 mm	>10 mm	Side-effects of treatment
1	70	F	1	4	RL	6	1100	0	3	Diarrhoea
2	51	F	1	0	RL	4	850	0	0	None
3	37	F	1	1	RO	4	800	0	1	Colic pain
4	62	F	1	0	RL	5	1000	0	0	None
5	76	F	1	3	RL	6	1400	0	2	Vomit
6	38	F	1	0	RL	6	3000	0	0	None
7	43	M	1	2	RO	8	700	0	1	None
8	31	F	1	0	RL	4	1500	0	0	Diarrhoea
9	54	F	0	1	RL	7	1400	0	1	Diarrhoea
10	39	F	0	1	RO	6	1200	0	1	None
11	63	F	1	0	RL	12	700	0	0	None
12	49	M	1	2	RO	5	2100	0	1	Vomit
13	57	M	0	1	RL	6	1300	0	1	None
14	65	F	2	1	RL	8	1000	1	1	Diarrhoea

* RL, radiolucent; RO, radio-opaque

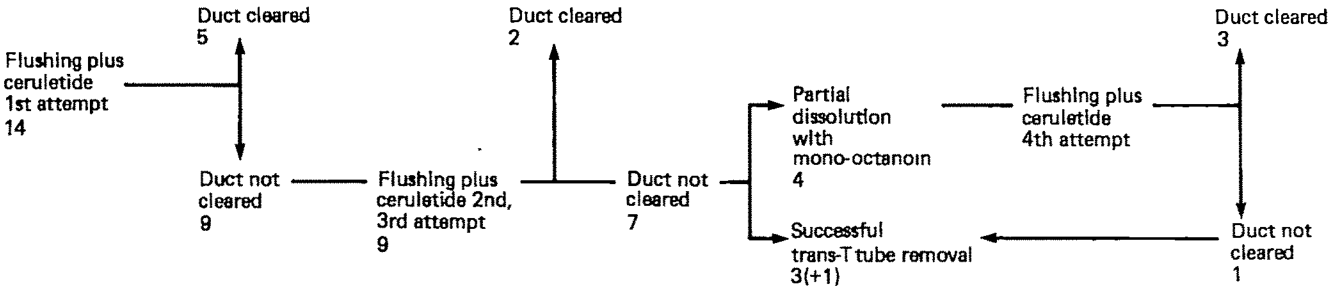
Flushing plus ceruletide 1st attempt 14
Duct cleared 5
Duct not cleared 9
Flushing plus ceruletide 2nd, 3rd attempt 9
Duct cleared 2
Duct not cleared 7
Partial dissolution with mono-octanoin 4
Successful trans-T tube removal 3(+1)
Flushing plus ceruletide 4th attempt
Duct cleared 3
Duct not cleared 1

Figure 1 *Treatment of retained CBD stones after cholecystectomy in 14 patients with biliary T tube*

Results

At the first attempt, the intraductal infusion of saline together with the intravenous administration of ceruletide induced the clearance of 15 out of 28 retained stones (*Table 1*). Passage of concretions was documented in 11 subjects (79 per cent) with complete clearance of the duct in 5 (36 per cent). Eleven of the cleared concretions had a diameter <10 mm, whereas the majority of stones refractory to the first treatment exhibited a diameter >10 mm. No severe complications were noted during the procedure. Some patients developed minor side-effects which settled spontaneously in 1–2 h. Bile cultures were always negative following the stone clearance.

Those patients who had a complete clearance of the concretions were discharged on the second day following the procedure. Patients with residual stones underwent one or two additional attempts with the same procedure which resulted in a complete duct clearance in two further cases (*Figure 1*). The mean total period of hospitalization of these seven patients was 4·1 days (range 3–8 days).

The other seven subjects were considered to be refractory to this form of treatment and were divided into two groups according to the type of stones and the results of the *in vitro* dissolution test with mono-octanoin: accordingly, four patients received mono-octanoin. The mean duration of mono-octanoin administration was 7·5±0·8 days (range 6–10 days) and the mean volume of the compound infused was 602±88 ml (range 430–850 ml). The side-effects of the litholytic therapy were minor (diarrhoea, abdominal cramps) and they responded to a decrease in the rate of infusion or to brief interruptions of the infusion. Mono-octanoin administration was interrupted when the diameter of the CBD stones appeared to be reduced to 10 mm or less. Thereafter, another treatment with ceruletide plus flushing was attempted, resulting in complete clearance in three cases. The three patients with radio-opaque stones underwent trans-T tube removal of residual concretions. The mean total hospital stay, from the first day of admission, was 16 days (range 14–18 days) and 9 days (range 8–11 days), for patients treated with mono-octanoin or T-tube extraction, respectively.

Discussion

Biliary tract surgery is the most frequently performed type of abdominal operation in Western countries[13]. Approximately 15 per cent of patients operated upon for cholelithiasis also have concomitant choledocholithiasis[13]. Most bile duct concretions are adequately treated during the primary procedure, but about 10 per cent of patients with duct stones do not have all their concretions removed at the time of cholecystectomy and bile duct exploration[1]. Because re-exploration is associated with a high risk of major side-effects, many non-invasive alternatives have been developed[4]. In this regard, attempts have been made to flush residual stones out with saline or solvents such as sodium cholate, but these methods have not gained general acceptance[6] Another approach was the infusion of mono-octanoin, which proved to be moderately effective in dissolving radiolucent CBD stones[14]. On the other hand, preliminary experience with methyl *tert*-butyl ether, an excellent *in vitro* solvent of cholesterol, was disappointing because of the difficulty of maintaining an adequate stone–solvent contact[15]. Recently, ceruletide has been used to relax the sphincter of Oddi, allowing large volumes of saline to be flushed down the T tube[7,8]. This favours a short phase of enhanced washout of the biliary tree which should induce the passage of residual stones into the gut. The technique is feasible for both radiolucent and radio-opaque stones and is mainly eligible for single or multiple stones of diameter < 10 mm.

Our results indicate this this method is successful in clearing residual stones in about 50 per cent of cases. This figure is within the range of success reported by Cuschieri[7,8] and does not seem to differ from the success rate reported with previous methods, which employed saline washout together with the administration of anticholinergic drugs[16–18] or glucagon[19]. In our experience, the morbidity related to the procedure of flushing plus ceruletide was only minor and no patient developed pyrexia even if antibiotics were not routinely used in this series. We believe that the post-washout fever described by others[17,18] was caused by excessive pressure in the biliary tract induced by perfusion. Accordingly, our suggestion is that the infusion pressure should never exceed 30 cmH_2O as this would produce back diffusion of potentially infected material into the sinusoids. Moreover, we recommend a low infusion rate of the saline into the choledochus also to prevent whirling effects which could endanger the disposal of the concretions.

In this series, only three out of fourteen patients had the procedure performed within 4 weeks of operation, but this represented delay in referral rather than reluctance to use the flushing at an early stage. Accordingly, we recommend flushing with saline and intravenous ceruletide on the day following an early postoperative cholangiogram showing retained biliary stones. If unsuccessful, the procedure should be repeated 24 and 48 h later. Large radiolucent stones may be partially dissolved with intraductal instillation of mono-octanoin and then eliminated by flushing. This approach allowed us to reduce both the amount and the time of mono-octanoin administration. If we compare the mean volume and the average time of mono-octanoin infusion with the values obtained in a previous investigation performed by our group[12], we find a decrease of 29 per cent (602 *versus* 848 ml) and 46 per cent (7 *versus* 13 days), respectively.

Persisting radio-opaque stones were removed via the T tube. We selected this approach as the patients were treated at least 6 weeks after surgery when a mature sinus tract had formed around the T tube[20]. The success rate reported in this small series of patients does not underestimate the difficulties involved in this procedure, which requires skill and may be burdened by technical problems due to T-tube size and placement. Therefore, we did not consider the reduction in mean hospital stay of patients treated with T-tube extraction in respect to mono-octanoin large enough to justify the adoption of this technique as first-line treatment for large radiolucent concretions.

Endoscopic sphincterotomy might provide an appropriate and relatively safe alternative to T-tube extraction in the early postoperative period, i.e. within 4 weeks of surgery[21], but we did not employ this endoscopic method in the group of patients described here.

In conclusion, our results suggest that flushing combined with ceruletide is a safe and simple approach to the therapy of residual biliary stones which are lying below the T tube. This study did not show a clear advantage for this approach over saline flushing alone, so that a prospective randomized trial is warranted. In our opinion, flushing plus ceruletide should be attempted immediately after an early postoperative cholangiogram shows retained biliary calculi and, if unsuccessful, should be repeated in the following days. In order to reduce the size of large radiolucent stones, the technique may be combined with the intraductal instillation of mono-octanoin. Radio-opaque stones refractory to flushing can be removed by T-tube extraction or by endoscopic sphincterotomy and retrograde extraction.

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Anergy in jaundiced patients

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A prospective study of delayed hypersensitivity was carried out in jaundiced patients. One hundred and nineteen subjects were studied. Fifty-nine were controls and sixty were patients with pancreatobiliary pathology and biliary tract obstruction. A Multitest technique was used to evaluate the delayed hypersensitivity response, classifying the subject into one of three groups: immunocompetent, relatively anergic and anergic. In the control group, 76 per cent of the subjects were immunocompetent as opposed to 17 per cent of the patients ($P<0{\cdot}001$)*. Ten per cent of the control subjects and fifty-five per cent of the patients presented anergy* ($P<0{\cdot}001$)*. Amongst the patients no difference could be found in the index of anergy between malignant or benign pathology. A greater incidence of postoperative septic complications in anergic and relatively anergic patients was found. Our study indicates a relationship between jaundice and anergy.*

Keywords: Jaundice, hyperbilirubin, anergy, delayed hypersensitivity response

Jaundice is one of the most important risk factors for the development of postoperative sepsis, substantially increasing morbidity and mortality[1–4]. Several studies[5–10] have shown a relationship between pre-operative anergy and the development of postoperative infection in surgical patients.

We therefore evaluated the status of cell mediated immunity, and thus the incidence of anergy, in surgical patients presenting with biliary–pancreatic pathology and jaundice.

Patients and methods

A total of 119 subjects (59 control and 60 jaundiced patients) were prospectively studied over a 3-year period (1984–1986).

The control group consisted of 59 healthy subjects (30 men and 29 women) in good physical condition, with no history of recent weight loss and on no medication. The age range was 55–82 years (mean age ± s.d., 63·7 ± 6·8 years).

The patient group consisted of 60 subjects (33 men and 27 women) with pancreatobiliary tract obstruction and jaundice: 22 with carcinoma of the head of the pancreas, 23 with choledocholithiasis, 5 with cancer of the biliary tract, 5 with acute cholecystitis, 2 with tumours of the ampulla of Vater, 1 with chronic pancreatitis, 1 with 'Odditis' and 1 with cholelithiasis. Ages ranged from 28 to 83 years (mean age ± s.d., 66·7 ± 11·9 years). None had undergone surgery or received radiotherapy or chemotherapy in the 3 months preceding the study.

To evaluate cell mediated immunity the Multitest technique was used This method involves synchronous multipuncture of seven antigens and a glycerol control The seven antigens (each administered at a dose of 0 03 ml) were tetanus, 550 000 Merieux units/ml, diphtheria 1 100 000 MU/ml, Streptococcus (group C) 2000 MU/ml, tuberculin 300 000 units/ml, Candida 2000 MU/ml, tricophyton 150 MU/ml and *Proteus mirabilis* 140 MU/ml The control consisted of a 70 per cent weight/volume solution of glycerol.

Antigens were injected in the volar surface of the forearm and results were read at 48 h. Responses were considered positive when the average of the largest and smallest diameters of the weal was greater than 2 mm. The sum of the average diameters of the response to the seven administered antigens gives the individual score for each subject. Three response types were identified: immunocompetent (IC), with a score greater than 10 mm in men and 5 mm in women, relative anergy (RA), with a score from 2 to 5 mm in women and 2 to 10 mm in men; and anergy (A) with a negative response or a score lower than 2 mm.

The development of major sepsis in the 52 patients who underwent surgery was evaluated.

Six of the anergic patients were tested on several occasions to follow the relationship between the delayed hypersensitivity response on the one hand and bilirubin values and jaundice on the other. The subjects chosen were those available for testing, either because of a prolonged pre-operative hospital stay or because they lived nearby.

Statistical analysis was carried out by means of the χ^2 test with Yates's correction. Values of $P \leqslant 0{\cdot}05$ were considered significant.

Results

Of the 59 control subjects studied, 76 per cent were IC, whereas only 17 per cent of the patients presented an adequate cell mediated immune response ($P<0{\cdot}001$). Likewise, only 10 per cent of the controls presented anergy, as opposed to 55 per cent of the patients ($P<0{\cdot}001$). In all, 14 control subjects and 50 patients presented either anergy or relative anergy ($P<0{\cdot}001$) (*Table 1*).

An analysis of the delayed hypersensitivity response in relation to the diagnosis in the patient group showed no difference in the anergy index between patients with benign pathology and those with cancer. The anergic index ranged from 40 to 80 per cent and the anergy plus relative anergy index from 78 to 100 per cent (*Table 2*).

Of the 60 patients studied, 8 did not undergo surgery (1 IC, 2 RA and 5 A). Of the other 52, 1 anergic patient died intraoperatively. Of the remaining 51 patients 1 (11 per cent) of the 9 IC patients developed a pulmonary infection; 7 (47 per cent) of the 15 RA patients developed major postoperative sepsis (2 right subphrenic abscesses, 3 bacteraemia, 2 septic shock and death), as did 10 (37 per cent) of the 27 A patients (1 pulmonary infection, 4 bacteraemia and 15 septic shock with death).

In six patients with various different conditions (three with choledocholithiasis, two with neoplasm of the head of the pancreas and one with chronic pancreatitis) the delayed hypersensitivity response was found to return to normal once the biliary obstruction resolved or the bile was shunted, and the serum bilirubin returned to normal. It is important to note that despite the fact that four of the six patients were over 60 years old and two had inoperable tumours, immunocompetence was none the less restored.

Discussion

Surgery in the jaundiced patient is high-risk surgery accompanied by high morbidity and mortality, including such

Table 1 *Delayed hypersensitivity response*

	Control group ($n=59$)	Patients ($n=60$)	χ^2	P
Immunocompetent	45 (76)	10 (17)	40·17	<0·001
Relative anergy	8 (14)	17 (28)	3 24	n.s.
Anergy	6 (10)	33 (55)	17 62	<0 001
Relative anergy plus anergy	14 (24)	50 (83)	35·12	<0 001

Values in parentheses are percentages

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Table 2 *Delayed hypersensitivity response according to patient's diagnosis*

	Immuno-competent	RA	A	RA+A
Cancer of the head of the pancreas ($n=22$)	3 (14)	7 (32)	12 (55)	19 (86)
Choledocholithiasis ($n=23$)	5 (22)	6 (26)	12 (52)	18 (78)
Cancer of the biliary tract ($n=5$)	1 (20)	1 (20)	3 (60)	4 (80)
Acute cholecystitis ($n=5$)		1 (20)	4 (80)	5 (100)
Ampulloma of the ampulla of Vater, 'Odditis,' chronic pancreatitis, cholelithiasis ($n=5$)	1 (20)	2 (40)	2 (40)	4 (80)

Values in parentheses are percentages. A, anergy; RA, relative anergy

serious complications as renal failure, gastrointestinal haemorrhage, coagulation disorders and defects in wound healing[11–13]. Furthermore, these patients have an increased incidence of infection in the postoperative period[1,3,4]. Several studies on bile bacteriology have pointed out the high index of positive bile cultures in jaundiced patients[14–16].

Independently, various authors[5–10] have established a close correlation between the presence of pre-operative anergy and the development of postoperative sepsis in surgical patients. However, the results are subject to discussion and the findings of Brown *et al.*[17] and Ausobsky *et al.*[18] do not corroborate this relationship.

In the present study we evaluated the delayed hypersensitivity response and the incidence of anergy in jaundiced patients, and the relationship between anergy and postoperative sepsis. Despite the fact that the presence of neoplasm is clearly related to anergy, no significant difference was observed between those patients with malignant disease and those with benign conditions: 86 per cent of patients with malignant disease of the head of pancreas and 80 per cent of those with biliary tract cancer presented either A or RA, as did 78 per cent of patients with lithiasis of the common bile duct, 100 per cent of those with acute cholecystitis and 80 per cent of those with other benign pathology. Although the small number of IC patients does not allow us to draw statistically significant conclusions, the increased incidence of postoperative sepsis in RA and A patients is clear, as is the more serious nature of their septic complications.

These results are important from a clinical standpoint, as pre-operative decompression of the biliary tract in anergic jaundiced patients may be indicated. Although the advisability of this procedure for all icteric patients is debatable[19–30]. Pain has pointed out that it can be useful in high-risk patients, including those with anergy. Gouma *et al.*[32] have very recently shown that internal biliary drainage significantly decreases the incidence of septic complications compared with external biliary drainage. They attribute this to the 'replacement of bile into the intestinal tract and re-establishment of the enterohepatic cycle of bile salts that is associated with internal drainage'. They note that endotoxaemia reported in biliary obstruction has been linked by others to the absence of bile salts in the intestinal tract, and suggest that this could be aggravated by external biliary drainage.

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Short note

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Peroperative cholangiography: needle puncture of the hepatic duct versus cannulation of the cystic duct

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Operative cholangiography may be performed by either cannulation of the cystic duct or needle puncture of the common hepatic duct. Evans and Jenkins[1] retrospectively compared the two methods and found no difference in terms of diagnostic accuracy and postoperative morbidity. We have prospectively evaluated cannulation of the cystic duct and needle puncture of the common hepatic duct in a randomized series of 176 patients who underwent cholecystectomy. A total of 157 patients had a cholangiogram but this was deemed inappropriate in the other 19 cases.

Patients and methods

There were 135 women (mean age 53 years) and 41 men (mean age 59 years). In all, 88 patients underwent needle puncture of the common hepatic duct, and 69 were randomized to undergo cannulation of the cystic duct which was unsuccessful in 9 cases. Needle puncture was performed by oblique puncture of the common hepatic duct with a 22 gauge needle. A single injection of 8 ml of 30 per cent Hypaque (Sterling Research) was given and two films were exposed. Cannulation was performed with a Stoke-on-Trent (Portex) catheter. Two films were exposed after the injection of 3 ml and then a further 5 ml of contrast.

The cholangiograms were assesed independently by a radiologist (W.T.E.) and 2 surgeons (M.D., E.S.K.). Masking tape was applied to all the cholangiograms to conceal the method used. The cholangiograms were awarded three scores, from one to ten, for the visualization of the intrahepatic ducts, common bile duct and ampullary region, respectively.

Results

Choledochotomy was carried out in 28 of the patients who had a cholangiogram (needle puncture, 20; cannulation, 8) and these patients all received intravenous cephazolin peroperatively and for 48 h afterwards. In three cases no stones were recovered (two needle puncture and one cannulation). Two patients who were thought to have a normal needle cholangiogram later presented with a proven residual stone. Those patients who had a choledochotomy were excluded from the analysis of postoperative drainage, wound infection and pyrexia.

The mean volume of peritoneal drainage after needle puncture (243 ml) was significantly greater than for cannulation (115 ml; $P<0\cdot001$, Student's t test). Two needle puncture patients underwent reoperation for bile leakage but this could not be directly attributed to the needle puncture (choledochotomy, accessory bile duct). The overall incidence of wound infection (discharge of pus) was 5 per cent. The incidence of both wound infection and postoperative pyrexia ($\geqslant 37\cdot5$°C) was not significantly different between the groups.

Table 1 *Mean cholangiogram scores for the intrahepatic ducts, common bile ducts and ampullary region according to a radiologist (WTE) and two surgeons (M.D., E.S.K.)*

	W.T.E.		E.S.K.		M.D.	
	NC	CC	NC	CC	NC	CC
IHD	7·3	8·0	6·7	7·1	6·2	6·7
CBD	8·2*	9·1*	6·6	7·0	7·2	7·6
AR	7·2*	9·0*	7·2*	8·4*	7·4	8·2

NC, needle puncture of the common hepatic duct; CC, cannulation of the cystic duct; IHD, intrahepatic ducts; CBD, common bile duct; AR, ampullary region. *Significant difference $P<0\cdot03$ between NC and CC

The mean cholangiogram scores were consistently higher for cannulation than needle puncture(*Table 1*), and this difference was significant for the visualization of the common bile duct and ampullary region ($P<0\cdot03$, unpaired t tests). In each of the cannula cholangiograms the intrahepatic ducts, common bile duct and ampullary region were all visualized, but there were eleven needle cholangiograms in which one or more segments of the biliary tree were not seen, either owing to non-filling or extravasation of contrast. We compared the incidence of filling defects which could not be explained by stones found at choledochotomy or diagnosed on subsequent clinical follow-up. This varied from 8 to 10 per cent for needle puncture and 16 to 20 per cent for cannulation, which suggests that the risk of introducing air bubbles may not be confined to cannulation.

Discussion

Turunen *et al.*[2] reported high postoperative drainage volumes with needle puncture and this has been confirmed. Previous reports on needle puncture[2–4] fail to report a single instance of bile accumulation in 1315 patients all of whom underwent peritoneal drainage. Prolonged bile leakage because of the presence of undiagnosed distal obstruction remains a theoretical risk which is heightened by the poor visualization of the lower end of the common bile duct which occurred in 12 per cent of needle cholangiograms. Needle puncture of the cystic duct avoids bile leakage and gave reliable results in a series of 442 cholecystectomies[5]. We conclude that cannulation of the common hepatic duct is the better method, but when this is not possible needle puncture of the cystic duct accompanied by peritoneal drainage is an acceptable alternative.

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150–153

Operative management of tubulovillous neoplasms of the duodenum and ampulla

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Six patients are described to illustrate the operative management of tubulovillous neoplasms of the duodenum. Pancreaticoduodenectomy is appropriate for associated invasive carcinoma. Transduodenal submucosal excision of tubulovillous neoplasms with resection and reconstruction of the distal bile and pancreatic ducts if necessary is a satisfactory alternative when the neoplasm has not penetrated the muscularis mucosae.

Keywords: Tubulovillous neoplasm, duodenum, ampulla, surgery

The duodenum is the second most common site, after the large bowel, of tubulovillous neoplasms of the gastrointestinal tract. Such tumours are, however, uncommon, less than 100 having been reported in the world literature[1]. Excision is mandatory because of a 30–85 per cent[1–4] risk of malignant transformation but may be complicated if there is a close relationship to the papilla of Vater or by extension to involve the ampullary mucosa.

A series of six patients with tubulovillous or villous neoplasms of the duodenum treated since 1983 illustrate aspects of operative management.

Case reports

Case 1

A 70-year-old woman presented in July 1983 with diarrhoea and epigastric pain. Large bowel investigation was negative but duodenoscopy showed a villous tumour in the first part of the duodenum. Superficial biopsies were benign and the extent of the lesion was subsequently demonstrated on hypotonic duodenography (*Figure 1*). At laparotomy the duodenal bulb was opened and after infiltration with adrenaline solution a 3 cm tumour was excised in the submucosal plane with a margin of normal mucosa. The mucosal defect was closed with a continuous absorbable suture of 4/0 polydioxanone. Histologically the lesion was a benign tubulovillous adenoma. Endoscopic follow-up 2 years later showed no recurrence.

Case 2

A 51-year-old man presented in May 1986 with anaemia. Duodenoscopy showed a large tumour of the proximal second part of the duodenum. Superficial endoscopic biopsies were benign but at operation palpation through the intact duodenal wall suggested fixity of the mucosa. Segmental excision of the duodenum proximal to the ampulla with a single layer end-to-end duodeno–duodenal anastomosis was carried out in preference to submucosal dissection. There was, however, no histological evidence of malignant infiltration: the tubulovillous adenoma was benign. There was no evidence of recurrence at endoscopy 6 months later.

Case 3

A 71-year-old woman presented with nausea, malaise and jaundice in June 1983. An ultrasonic scan showed a moderately dilated biliary tree with a possible distal tumour mass. Hypotonic duodenography showed a periampullary tumour (*Figure 2*) which was confirmed on endoscopy. The tumour was thought to be a carcinoma of the ampulla but superficial biopsies were benign. At operation the duodenum was opened longitudinally and, after submucosal injection of adrenaline solution, the affected mucosa along with the ampulla and distal bile and pancreatic ducts were excised. The tumour extended 2 cm into the bile duct. The biliary and pancreatic ducts were sutured together and the duodenal mucosal defect closed around them using interrupted 4/0 polydioxanone sutures. Recovery was uneventful and the patient remains well with no evidence of recurrence. Histology of the resected specimen showed a tubulovillous adenoma.

Case 4

A 66-year-old man presented with episodic jaundice in October 1983. On ultrasonography the bile ducts were dilated with an abrupt distal 'cut off' and an appearance of intraluminal tumour. Duodenoscopy showed a tumour at the ampulla which was again thought to be a carcinoma but superficial biopsies were benign. Retrograde cholangiography showed a proliferative tumour obstructing the distal common bile duct (*Figure 3*). At operation the appearances were almost identical to those in case 3 and a similar procedure of submucosal excision of the affected mucosa, mobilization, excision and reconstruction of the bile and pancreatic ducts was performed. Histology of the resected lesion showed a benign tubulovillous adenoma. The patient remains well with no evidence of recurrence.

Case 5

A 67-year-old man presented in July 1984 with septicaemia secondary to acute calculous cholecystitis and was managed conservatively. On ultrasonography moderate bile duct dilatation was evident and liver function tests were deranged. Six weeks later at interval cholecystectomy operative cholangiography showed an irregular filling defect in the distal bile duct with appearances like those in *Figure 3*. The findings on opening the duodenum were again similar to those in cases 3 and 4 with a tubulovillous adenoma of the duodenum extending into the ampulla. A similar submucosal excision with reconstruction of the ampulla was

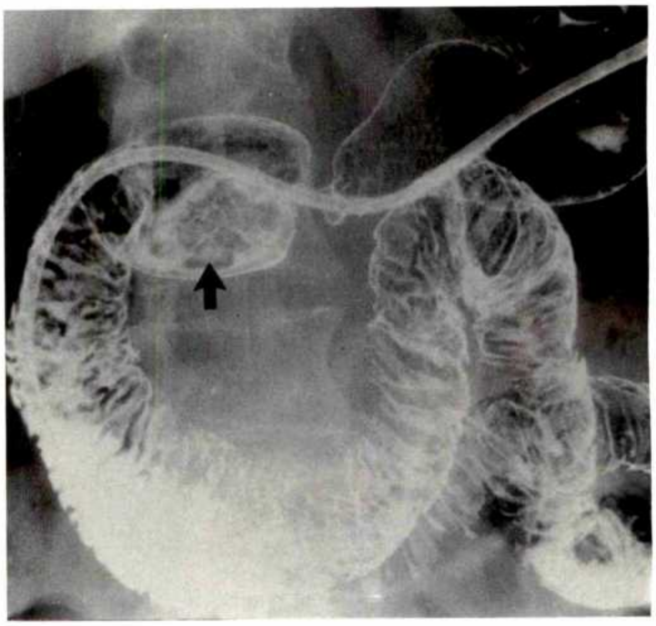

Figure 1 *Case 1, hypotonic duodenogram showing a filling defect in the duodenal bulb (arrowed)*

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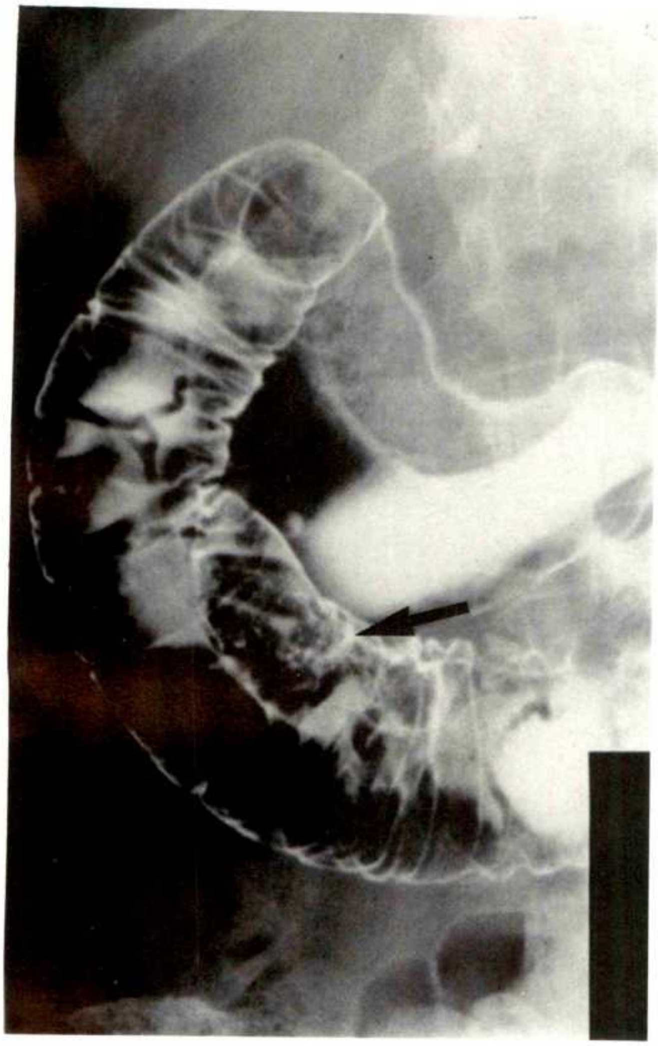


Figure 2 *Case 3, hypotonic duodenogram showing a periampullary neoplasm (arrowed)*

performed. Recovery was uncomplicated and the patient remains well with no evidence of recurrence. Histology showed a benign tubulovillous adenoma involving the ampulla and distal bile duct.

Case 6

A 58-year-old man who had previously undergone cholecystectomy in 1975 presented in June 1986 with obstructive jaundice. Ultrasonography showed a dilated biliary tree and on duodenoscopy an ulcerating tumour at the ampulla was seen. Retrograde cholangiography was unsuccessful demonstrating only the pancreatic duct. Biopsies showed adenocarcinoma. At operation there was no evidence of metastatic spread and a firm nodule measuring approximately 1 cm in diameter was palpable at the ampulla. A pylorus-preserving pancreaticoduodenectomy was performed. On opening the resected specimen a circumferential villous neoplasm extending over approximately 8 cm of the duodenal wall with a small central ulcerated area at the ampulla was found. Histology showed a villous adenoma of the duodenal mucosa with malignant transformation and infiltration at the ampulla. A single lymph node in the resected specimen contained a microscopic focus of metastatic carcinoma. Six months later the patient had multiple hepatic metastases and local recurrence.

Discussion

The diagnosis of duodenal neoplasm was established pre-operatively in all but one of these patients (case 5) with symptoms of biliary obstruction, anaemia secondary to gastrointestinal haemorrhage or vague dyspepsia. Both hypotonic duodenography and endoscopy were useful and may be regarded as complementary in the investigation of duodenal tumours. In one patient (case 6) an extensive circumferential duodenal lesion was overlooked at endoscopy probably because of its uniform appearance although the area of ulceration secondary to malignant change was recognized.

Duodenal adenomas have been described in conjunction with familial colonic polyposis but there was no such association in any of these patients.

In five of the six cases histology showed a mixed tubular and villous appearance. Smooth muscle cells were often seen to have been drawn into the connective tissue of the base between the fronds of neoplastic cells, presumably as a result of repeated mucosal prolapse. These tubulovillous lesions were benign but they have a recognized malignant potential intermediate between tubular and villous adenomas[4]. The greater malignant potential of pure villous neoplasms was exemplified by case 6. Superficial biopsies, whether obtained endoscopically or at laparotomy with frozen section, cannot be relied upon to exclude malignant change[4]. As in the colon it is probable that metastases do not occur until the muscularis mucosae is infiltrated[5]. Malignant change in a superficial biopsy, therefore, is not in itself an indication that local resection is inappropriate.

The size and largely sessile nature of such neoplasms makes endoscopic removal unattractive except possibly in the smallest of lesions. The decision for or against a radical procedure depends on the clinical appearance of the tumour: areas of ulceration, induration or apparent fixity to the underlying muscle suggest malignancy and a need for more radical surgery[4]. Although segmental duodenal resection was carried out in one patient (case 2), submucosal excision would in retrospect have been both appropriate and simpler.

Submucosal excision is readily applicable to tumours remote from the ampulla including polyps due to localized hyperplasia of Brunner's glands but periampullary involvement extending into the bile duct complicates the situation. Local excision extended to include the ampulla and associated ducts has been thought hazardous because of the possibility of leakage[3,4]. Proximal choledocho–enteric anastomosis[6] or pancreatico-

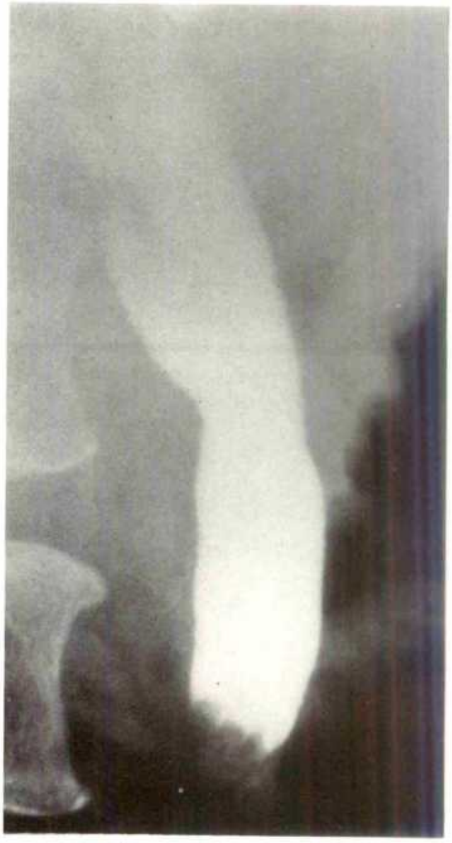
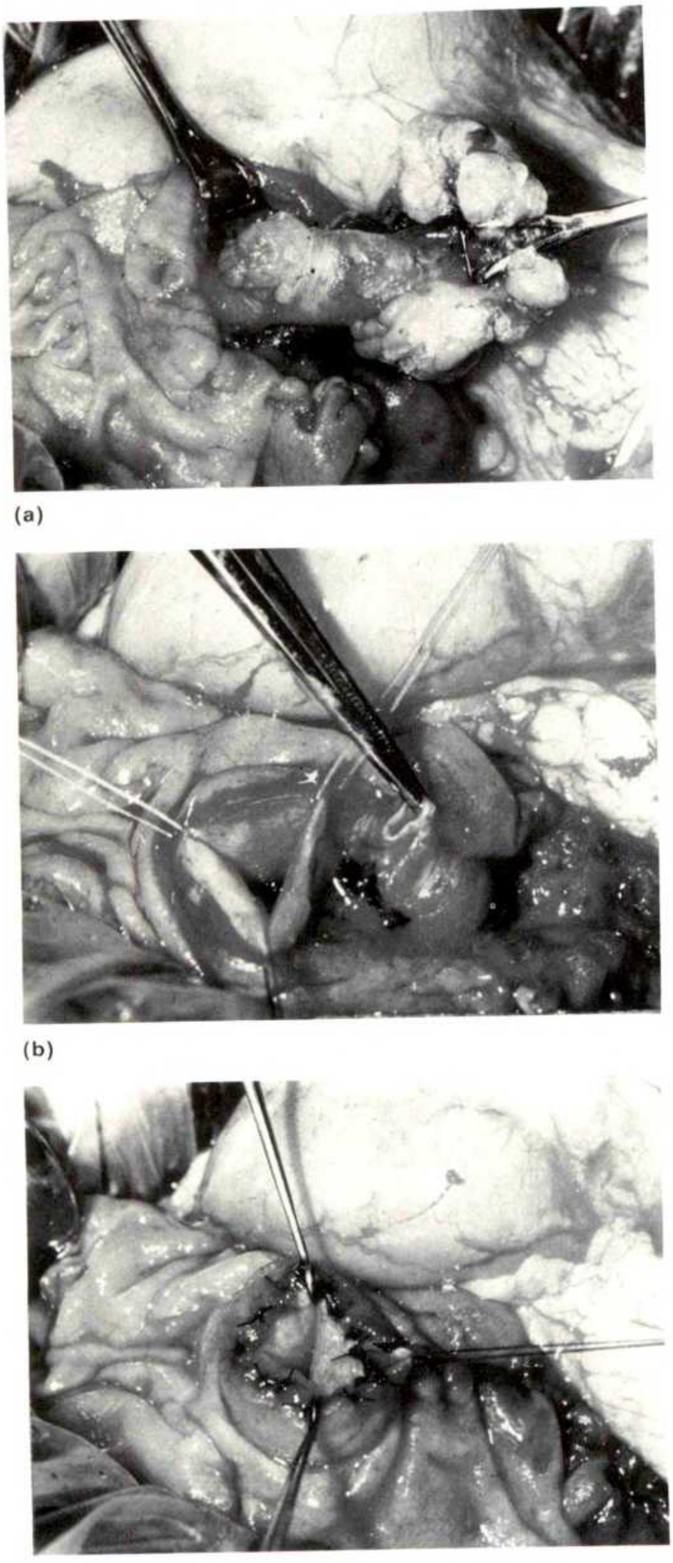


Figure 3 *Case 4, retrograde cholangiogram showing a proliferative neoplasm obstructing the distal common bile duct*


(a)

(b)

(c)

Figure 4 *Case 3:* **a**, *operative sequence showing submucosal mobilization of the duodenal mucosal tumour and the dilated distal common bile duct with protrusion of the intraluminal tumour at the point of division of the bile duct;* **b**, *appearance after excision of the neoplasm, distal bile and pancreatic ducts;* **c**, *reconstruction of the divided ducts and duodenal mucosa*

duodenectomy have been suggested as alternatives. In our experience submucosal excision of periampullary tumours extending into the ampulla together with intraduodenal excision of the distal common bile and pancreatic ducts has been straightforward.

Steps in the technique are shown in *Figures 4* and *5*. After

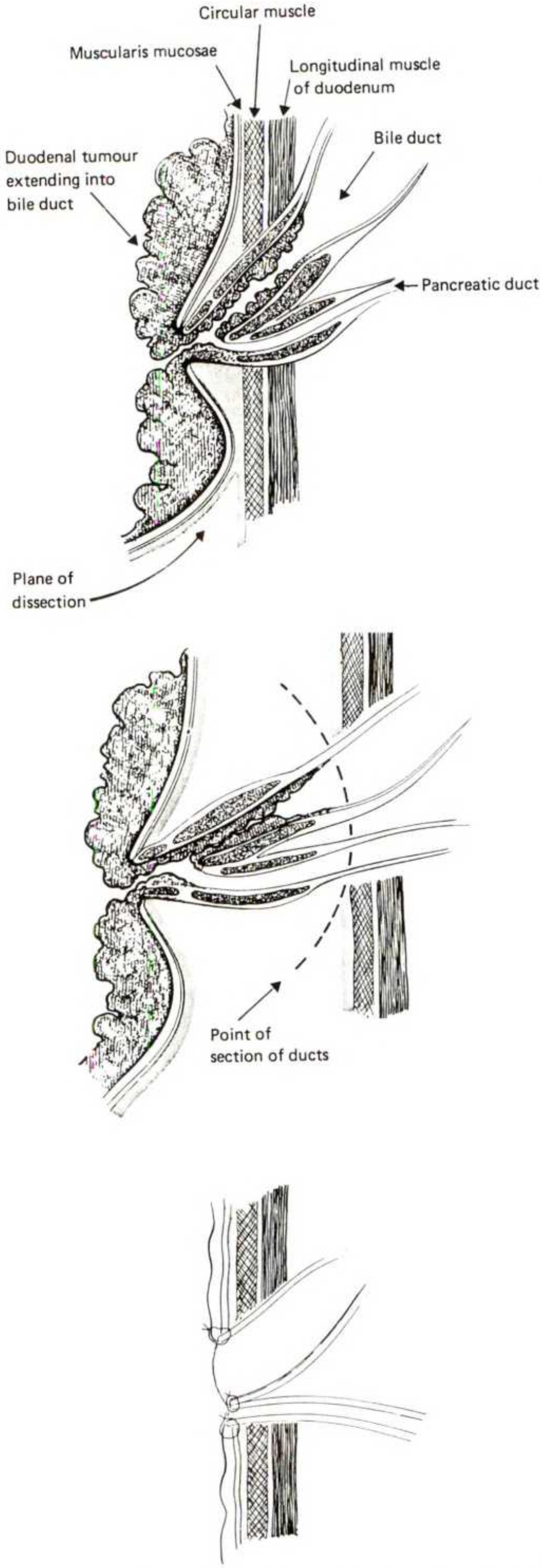

Circular muscle
Muscularis mucosae
Longitudinal muscle of duodenum
Bile duct
Duodenal tumour extending into bile duct
Pancreatic duct
Plane of dissection
Point of section of ducts

Figure 5 *Diagram showing excision of periampullary tumour extending into common bile duct*

submucosal infiltration of 1:200000 adrenaline solution the duodenal component around the ampulla is circumcised and dissected in the submucosal plane. The distal common bile duct and pancreatic duct are readily delivered through the muscular wall of the duodenum in a manner and plane analogous to transvesical mobilization of the distal ureter. The amputated bile and pancreatic ducts are co-apted and the duodenal mucosal defect is closed with interrupted sutures to the resulting common ostium. This technique was used in cases 3, 4 and 5 without complication. During follow-up over 3–4 years there has been no evidence of local recurrence or biliary obstruction. We have used 4/0 polydioxanone for reconstruction and the same material is used for continuous longitudinal closure of the duodenum in either one (serosubmucosal) or two (mucosal and serosubmucosal) appositional layers.

Local excision and reconstruction of the ampulla was probably first described by Halsted in 1899[7], although its use for malignant disease, and its applicability for benign tubulovillous adenomas, especially those extending into the bile duct, has not previously been emphasized. It is also a possible alternative in patients thought unsuitable for a more radical operation when malignant change appears localized. This useful and fairly simple operation is not described in any of the standard textbooks on operative surgery.

In the single patient in this series in whom a pre-operative diagnosis of malignancy was made (case 6), a pylorus-preserving pancreaticoduodenectomy was performed. This variant of Whipple's procedure was reintroduced in 1978[8] to avoid the postoperative morbidity associated with gastric resection. Increasing experience with the procedure suggests that it succeeds in this aim without compromising the radical nature of the operation[9]. Unfortunately in this patient recurrent disease in the liver and abdomen appeared within 6 months of resection.

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Total pancreatectomy in the MEN-1 syndrome

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A family with the multiple endocrine neoplasia Type 1 (MEN-1) syndrome, followed over three generations, is presented. In the first generation, one family member died after a history indicating Zollinger–Ellison syndrome. In the second generation endocrine pancreatic tumours were diagnosed or suspected in three out of five members. In the third generation, five out of seven members were investigated and four of these had positive tests at hormonal screening. Of particular diagnostic value in this family was the determination of peripheral serum levels of proinsulin and C-peptide, which were used as tumour markers both for diagnosis and in the postoperative follow-up. Two members in the third generation have been successfully managed by total pancreatectomy. A MEN-1 patient with malignant pancreatic tumours should be considered for total pancreatectomy if the pancreatic disease has caused high morbidity and mortality within the family. This is especially pertinent if the patient has multiple malignant tumours.

Keywords: MEN-1, total pancreatectomy, insulinoma, proinsulin, C-peptide

The multiple endocrine neoplasia Type 1 (MEN-1) syndrome is characterized by simultaneous occurrence of tumours and/or hyperplasia in the pituitary gland, parathyroids and endocrine pancreas. This syndrome is inherited as an autosomal dominant trait[1]. Friesen[2] reported in 1983 on six members of four separate MEN-1 families with pancreatic endocrine tumours. Welbourn[3] found that 8 per cent of pancreatic endocrine tumours were manifestations of the MEN-1 syndrome. Gastrinomas occurred most frequently, followed by insulinomas and VIP-omas. The main cause of death among affected members of MEN-1 families was manifestations of the endocrine pancreatic tumours. Histological features such as nuclear pleomorphism, mitotic activity and local invasion are less reliable indicators of tumour aggressiveness[4]. The malignant behaviour of the pancreatic tumours varies between different families. The family history is an important aid to prediction of the course of the disease.

When multiple endocrine tumours of the pancreas are present, the MEN-1 syndrome must be suspected and careful screening of family members is recommended[5]. Friesen and colleagues[6] pointed out the possible diagnostic value of immunohistochemical examination of antral biopsies in the screening of a MEN-1 family in order to demonstrate hyperplasia of G cells. Elevated peripheral levels of pancreatic polypeptide (PP) were reported to be a useful marker in the search for pancreatic islet disease[6,7].

The aim of this report is to describe the pancreatic manifestations of MEN-1 in a family followed over three generations. Each generation has received different modes of therapy according to the knowledge available at the time. In the surgical treatment of the third generation, our intention was to treat the pancreatic tumour radically, thereby hoping to improve the prognosis.

Methods

Processing of surgical specimens

The tissue specimens obtained at surgery were routinely fixed in 10 per cent buffered formalin and/or Bouin's fluid. Sections 5 μm thick were stained with haematoxylin–eosin, the argyrophil technique of Grimelius[8,9] and the peroxidase–antiperoxidase (PAP) immunohistochemical technique[10], using the following antisera: insulin, glucagon/glicentin, pancreatic polypeptide (PP), somatostatin, vasoactive intestinal polypeptide (VIP), gastrin (C-terminal, tetragastrin), serotonin, substance P (SP), PYY, enkephalin (Leu- and Met-) and β-endorphin[11].

Assay of peptides and serotonin

Radioimmunoassays were used for the determination of the concentrations of the following peptide hormones: immunoreactive insulin (IRI), proinsulin, C-peptide, SP, gastrin, calcitonin, PP, glucagon, VIP, prolactin and α- and β-subunits of human chorionic gonadotrophin (HCG). Serotonin was assayed by liquid chromatography with electrochemical detection.

Patients and treatment

First generation (I)

The first family member with a probable MEN-1 syndrome was a women who died in 1953 at the age of 63 from a bleeding ulcer of the upper jejunum (*Figure 1*) She had calyceal calculi and renal impairment as well as an abdominal tumour. Her history indicates that she had hyperparathyroidism (HPT) and the Zollinger–Ellison syndrome (ZES) but, unfortunately, no tumour tissue was examined histologically As the linkage between pathology and symptoms was not understood at that time, no adequate treatment was instituted.

Second generation (II)

The second generation included five members, three women and two men, all treated at other hospitals. Only one woman (IID, born in 1920) is at present clinically free from disease and negative at hormonal screenings (*Figure 1*). One female member (IIC, born in 1918) has a

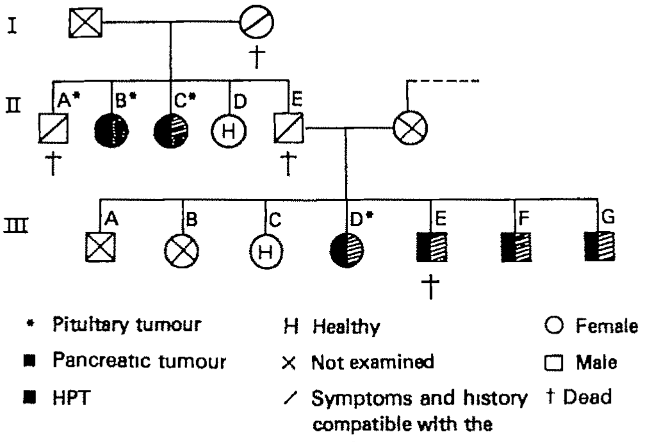

Figure 1 *Pedigree showing three generations of a MEN-1 family*

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Table 1 *Hormonal findings at selective catheterization of pancreatic veins and in peripheral veins before and after the third operation in patient IIIF*

Period	Location	IRI μU/ml	C-peptide pmol/ml	Proinsulin pmol/ml
Pre-operative (November 1982)	Peripheral vein	27 (0–18)	1·12 (0·18–0·78)	0·190 (0–0·036)
	ASPD vein		2·20	0·475
Postoperative: March 1983	Peripheral	5	<0·05	0·002
September 1983		176	<0·05	0
November 1986		—	<0·05	0

The peripheral levels of IRI and C-peptide were slightly elevated, while proinsulin showed a more pronounced increase. The levels detected in the hepatic veins were in the same range as the peripheral levels. However, sampling from pancreatic veins, e.g. the anterior superior pancreaticoduodenal vein (ASPD), demonstrated increased levels of both C-peptide and proinsulin. At follow-up after surgery, these markers have been undetectable. (Reference values within brackets)

Table 2 *Palliative treatment of patient IIIE after surgery and the response of peripheral tumour markers*

	Peripheral levels of proinsulin/C-peptide ($n < 0·036/0·78$ pmol/ml)	
Treatment	Before treatment	After treatment
Hepatic artery embolization November 1982	0·170/1·20	0·120/0·70 (2 weeks)
Interferon (induction + 6 million international units 5 days/week IM) April 1983	0·120/1·04	0·036/0·52 (7 months)
Streptozotocin (induction + 1 g/m^2 IV) April 1984	0·090/1·50	0·048/0·60 (2 weeks)

complete MEN-1 syndrome and is currently treated with streptozotocin for multiple pancreatic endocrine tumours with hepatic metastases. The third woman (IIB, born in 1925) probably also has a complete syndrome; gastrin and PP serum levels are elevated but no pancreatic lesions have been demonstrated surgically or radiologically. The two brothers died on the same night from pituitary bleeding (IIA, at the age of 36) and severe gastrointestinal bleeding (IIE, at the age of 52) respectively. The older brother (IIE) had renal calculi and uraemia and a pancreatic tumour, which was not examined histopathologically. His seven children make up the third generation.

Third generation (III)

The third generation involves three women and four men. Five of them have been examined with regard to the MEN-1 syndrome. Two have refused (IIIA, born in 1940 and IIIB, born in 1942) because of lack of symptoms (*Figure 1*). Of the five members examined, only one (IIIC, born in 1943) is asymptomatic and has normal levels of all peptide hormones determined. One member (IIID) had a complete MEN-1 syndrome with typical symptoms of an insulinoma. Three other members had no or only vague symptoms, such as anxiety, restlessness, slight sweating and tremor without relation to food intake. All four affected members had elevated serum levels of proinsulin, C-peptide and SP and are presented in detail below.

IIIF (born in 1952). This patient was our proband to this family. He had surgery for HPT in 1980. During his period of stay at the hospital, he complained of sweating, fatigue and mild facial flush. Investigation on suspicion of an insulinoma had been negative in 1979 (insulin: glucose ratio and fasting test). Persisting symptoms led to a CT scan, which showed a tumour (diameter 5 cm) in the tail of the pancreas. Angiography showed a vascular tumour. At surgery, there was a malignant tumour in the body and tail of the pancreas with adjacent lymph node metastases and extranodal growth; resection was performed. One year later, vague symptoms recurred and an infiltrative malignant tumour (diameter 2 cm) was excised. Six months later, the same symptoms recurred together with elevated peripheral levels of IRI, proinsulin and C-peptide. A CT scan and angiography were negative but selective catheterization of pancreatic veins demonstrated higher levels of IRI, proinsulin and C-peptide than were found peripherally (*Table 1*). The levels of these hormones in the hepatic veins equalled the levels in the peripheral veins. These results indicated the presence of persistent islet-cell neoplasia or hyperplasia. None of the radiological investigations undertaken indicated hepatic metastases. Reviewing the clinical course of this patient in 1983, we considered that the only rational approach was a completion total pancreatectomy by removal of the head region. The surgical specimen contained a microadenoma with glucagon-immunoreactive cells as well as hyperplasia of insulin and C-peptide immunoreactive cells. This patient is now free of symptoms and has undetectable levels of insulin and C-peptide (*Table 1*). His body weight is stable and he is working as an occupational therapist.

IIID (born in 1945). This patient developed a complete MEN-1 syndrome. She had symptoms typical of an insulinoma in 1972. Angiography indicated a vascular tumour (diameter 3·5 cm) in the tail of the pancreas. At surgery, resection of the tail was performed as well as enucleation of a cystic tumour of the head. Histology demonstrated an argyrophilic tumour without malignant criteria. A few cells showed C-peptide or glucagon immunoreactivity. She was free of symptoms for 9 years but then she started to gain weight and suffered attacks of tremor related to fasting. By that time, we knew that her brother (IIIF) had a MEN-1 syndrome and she was therefore recommended further investigation. Screening of peptide hormones in peripheral blood showed normal results except for prolactin. A CT scan showed enlargement of the head of the pancreas. At surgical exploration, a small argyrophilic tumour (diameter 1 cm) was resected. Minority cell populations showed C-peptide and somatostatin immunoreactivity. A larger cell population was non-reactive, when the other antisera were used. At follow-up in 1984, she was free of symptoms but had developed elevated peripheral levels of proinsulin and C-peptide. She has refused further investigation.

III-E (born in 1945). This patient is the dizygotic twin of IIID. Because of the clinical history of IIID and F, he was further investigated in 1981, although he had no symptoms of endocrine disease. Peripheral hormonal screening (at that time not including proinsulin and C-peptide) was normal except for moderately elevated levels of SP. A CT scan demonstrated a large tumour (diameter 5 cm) in the tail of the pancreas and multiple hepatic metastases in both lobes. Resection of the body and tail of the pancreas was performed, including regional lymph node metastases. The largest of the hepatic metastases were excised. The pancreatic tumour showed argyrophilia and the immunocytochemical survey demonstrated tumour cells with C-peptide, somatostatin, glucagon or enkephalin immunoreactivity. No positive immunoreaction with the insulin antibody was demonstrated. Eight months later, the patient's hepatic disease progressed rapidly, with elevated levels of proinsulin and C-peptide (*Table 2*). He was sequentially treated with embolization of the hepatic arteries[12], interferon[13] and finally streptozotocin[14]. No regression of the tumour mass was obtained after embolization. With interferon therapy (6 million international units of α-interferon 5 days/week) the liver returned to near normal size for 8 months. A similar effect was seen after addition of streptozotocin to interferon therapy (*Table 2*). Eight months later the patient became paraplegic, due to extension of skeletal metastases into the spinal canal. He succumbed to extensive tumour in October 1985.

IIIG (born in 1954). This patient had suffered from vague symptoms such as tremor and sweating, relieved by food intake, since 1980. The insulin:glucose ratio was within the normal range, as was the fasting test. Hormonal screening in 1982 of SP, proinsulin and C-peptide demonstrated elevated levels. Extensive radiological investigations did not reveal any pancreatic neoplasia. The positive findings with the 'familial' hormonal markers and the family history made us recommend surgical exploration Pre-operatively, he agreed to total pancreatectomy if malignant tumours were verified. At surgery, several small tumours (diameter 1–1·5 cm) distributed throughout the pancreas were found and verified by frozen section biopsy; total pancreatectomy was performed. Microscopically, tumour infiltration and frequent mitoses were found, indicating malignancy. No lymph node metastases were present. Islet cell hyperplasia was also found and the tumours demonstrated insulin immunoreactivity. This patient is now free of symptoms and has normal serum levels of islet hormones, 3½ years after the pancreatectomy. He is on insulin substitution and a fat-reduced diet and is supplemented with pancreatic enzymes. He has resumed his work as a car factory worker.

Discussion

In this family two members of the first two generations had pancreatic disease compatible with the Zollinger–Ellison syndrome. In the third generation the four affected members had elevated levels of proinsulin, C-peptide and SP; however, only one had manifest insulinoma symptoms. Elevated levels of IRI were recorded only in one patient (this assay was not available pre-operatively in the typical insulinoma patient). In this family assay of the hormonal markers, proinsulin, C-peptide and SP were necessary to establish the correct diagnosis. PP, which has previously been useful in the screening of MEN-1 families, was not elevated in any of the family members with pancreatic disease in the third generation in this family[6].

In the β-cells of pancreatic islets, insulin is formed from a large precursor molecule, proinsulin, which is cleaved into insulin and a connecting peptide (C-peptide). These two molecules are stored in granules until liberation. When released, insulin and C-peptide are liberated in equimolar concentrations but proinsulin is also released in minor amounts physiologically[15]. Proinsulin and C-peptide were better tumour markers in the peripheral circulation of our patients than IRI. This finding may correlate with the fact that only one out of four patients developed clinical signs of an insulinoma (IIID). The normal IRI levels in two patients (one with small tumours (IIIG) and one with extensive tumour disease (IIIE)) may indicate inhibited release of insulin from granules or enhanced peripheral metabolism of insulin. In one of these patients (IIIE), IRI was absent in the tumour at histological examination.

Insulinomas are usually small tumours, often 1–1·5 cm in diameter, which means that ultrasonography and CT scanning have been of limited diagnostic value[16]. These examinations, as well as angiography, were also negative in one of our patients (IIIG) with small tumours (diameter 1·5 cm). The diagnostic accuracy of angiography varies considerably but, in the series from the Mayo Clinic, insulinomas were visualized after selective injections and subtraction procedures in as many as 90 per cent of cases[16]. In one of our patients (IIIF) with pancreatic residual tissue, selective transhepatic catheterization of the portal venous system was performed with determination of the marker hormones[17]. Such sampling from small venous radicles of the pancreatic remnant revealed higher levels of C-peptide and proinsulin than in the hepatic veins or in the peripheral circulation. This indicated persisting islet-cell disease and also absence of hepatic metastases. Selective catheterization was also proposed in the second patient without clinical illness (IIIG). However, this patient had previously been subjected to angiography (with negative results) and was not willing to undergo this examination again, because of discomfort at the previous investigation. As not all insulinomas can be manually palpated at surgical exploration[18], he was informed about the possible need of frozen sections to establish the diagnosis at surgery[4].

Insulinomas are uniformly distributed throughout the pancreas and are usually solitary tumours[19]. However, in the MEN-1 syndrome multiple lesions have been demonstrated, as found in this study. In our patient with widespread disease, the surgical treatment was followed sequentially by embolization[12], interferon[13] and finally streptozotocin[14]. A marked objective remission was initially obtained with both interferon and a combination of interferon and streptozotocin. However, with the final progression of the hepatic disease and generalized skeletal metastases, no medical therapy was effective.

In our MEN-1 family, three of nine affected members died from their pancreatic tumours and two others had metastasizing pancreatic tumours. In one patient (IIIF), new tumours appeared due to the genetic defect, as long as there was residual pancreatic tissue left, which forced us to perform a completion pancreatectomy. This patient now has normal hormonal markers, is free of symptoms and works as an occupational therapist more than 6 years after the first operation, when a large pancreatic tumour and lymph node metastases with extranodal growth were excised.

Considering the serious prognosis of the pancreatic disease in this family, we found it justifiable to perform a total pancreatectomy in another family member at his first operation when we found malignant endocrine pancreatic tumours distributed throughout the pancreas. Because of its drawbacks, e.g. diabetes and steatorrhea, total pancreatectomy cannot be generally adopted as a treatment of pancreatic tumours in the MEN-1 syndrome. A MEN-1 patient with malignant pancreatic disease should be considered for total pancreatectomy if the pancreatic disease has caused high morbidity and mortality in the family. This is especially pertinent if the patient has multiple malignant pancreatic tumours.

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Short note

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Rupture of abdominal hydatid cysts

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Traumatic or spontaneous rupture of hydatid cysts is a rare complication which is difficult to diagnose before operation and which has a very high morbidity and mortality rate[1]. In this paper we present our experience with 15 cases of rupture.

Patients

A review of 471 patients who underwent surgical treatment for abdominal hydatid cysts in our hospital between 1965 and 1985 was carried out. Cyst rupture into the peritoneal cavity occurred in 15 patients (3·2 per cent). The median age was 32·2 years (range 11 to 71 years) and the male:female ratio was 7:8.

A history of trauma was obtained in five patients but a history suggestive of hydatid disease was present in only two patients There were 12 patients admitted through the emergency room with an acute abdomen and the remaining 3 patients came to hospital between 20 and 27 days after the onset of symptoms.

All of the patients experienced abdominal pain of variable localization and intensity. Nine patients presented with nausea, vomiting and signs of peritoneal irritation anaphylaxis, as manifested by a rash and urticaria, was found in six cases. Two patients presented with hypovolaemic shock after trauma to the liver and spleen. Another patient presented with both an acute abdomen and upper gastrointestinal haemorrhage. Palpable painful masses were found on examination of two patients with non-hepatic hydatid disease. All patients underwent surgery after appropriate correction of shock and fluid and electrolyte upsets

Results

Complicated hydatid disease was suspected pre-operatively in only three cases. One patient showed curvilinear calcification in the right upper abdominal quadrant on a plain abdominal film. Two patients had undergone surgery for hepatic echinococcosis 2 and 5 years previously. A total of 19 cysts were found at operation: in the liver (17 cysts), pancreas (1 cyst) and the omental bursa (1 cyst). In this last case the cyst had perforated into the posterior gastric wall. All of the hepatic cysts were superficial or 'iceberg' cysts. Only one patient presented with concomitant intrabiliary rupture and biliary ascites. In 13 patients peritoneal dissemination of 300 to 500 ml was found, and in 6 cases the fluid was purulent.

Of the 19 cysts, partial cystectomy was performed in 9 cases, total cystectomy in 4 and cyst evacuation and external drainage in another 4 cases. Hepatotomy with selective vascular ligation and suture of the inferior vena cava and right suprahepatic vein was carried out in one case. A Billroth II gastrectomy was performed in the patient with an omental bursa cyst penetrating the posterior gastric wall. All the cysts were sterilized with hydrogen peroxide and hypertonic saline solution. The peritoneal cavity was washed with 5000 ml saline solution.

During the postoperative period five patients developed complications: two developed an incisional hernia, one a bleeding stress ulcer, one a faecal fistula and one a pleural effusion with hepatic abscess. Three patients required urgent reoperation (one hepatic abscess and two incisional hernia).

The operative mortality was 6·7 per cent (one patient) and the median postoperative hospital stay was 45·6 days (range 11–164 days).

Thirteen patients were treated with mebendazole, 30–40 mg kg^{-1} day^{-1}, for a 3-month period. The duration of follow-up has ranged from 20 to 80 months (mean 52·5 months) All of the survivors were evaluated every 6 months by clinical examination, immunological testing, and ultrasound and CT examination. Re-intervention for disseminated abdominal disease has been necessary in two patients who had not been treated medically with mebendazole during a period when it was unavailable.

Discussion

Rupture of hydatid cysts into the abdominal cavity is a rare complication affecting from 2 to 12 per cent of patients with the disease. Rupture may affect younger patients and the median age of 32 years in this group contrasts with one of 41 years in patients with non-ruptured hydatid cysts[3]. The majority of cases present urgently with abdominal pain (100 per cent), signs of peritoneal inflammation (60 per cent) or evidence of anaphylaxis (40 per cent). Pre-operative diagnosis is difficult as rupture constitutes the first clinical manifestation of the disease in 80 per cent of cases. Urgent surgical intervention is still the treatment of choice. Total cystectomy is performed if possible depending on the location of the cyst and the clinical condition of the patient. In our opinion postoperative medical treatment is mandatory and mebendazole is currently the drug of choice.

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Pancreatitis and hyperparathyroidism

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Hypercalcaemia is considered to be a rare cause of pancreatitis but the true cause-and-effect relationship between hyperparathyroidism and pancreatic inflammatory disease remains controversial. Over 100 patients have been reported in whom both processes have occurred concurrently, but doubts have been expressed as to whether or not this association is due to chance. We report 10 new cases of hypercalcaemic hyperparathyroidism associated with different types of pancreatitis. Seven patients had primary hyperparathyroidism and three had hyperparathyroidism after renal transplantation. Two experienced acute pancreatitis after parathyroidectomy. Of the remaining eight patients, five had hypercalcaemia equal to or above 120 mg/l. The prevalence of pancreatitis in our series of 86 cases of primary hyperparathyroidism is 8 per cent. Acute and chronic calcifying types of pancreatitis were observed. Three patients died of the disease, two of them after renal transplantation. It is suggested that pancreatitis may complicate the clinical course of hyperparathyroidism, particularly when hypercalcaemia is moderate to severe and/or there are other risk factors such as treatment with steroids and azathioprine after renal transplantation.

Keywords: Pancreatitis, hyperparathyroidism, renal transplantation

Acute and chronic pancreatitis have been commonly reported in association with primary hyperparathyroidism (HPT). Recent publications have cast some doubt on the alleged association and any cause and effect relationship between these two diseases[1]. We add some new data to this controversy by reporting our experience in ten patients with pancreatic inflammatory disease associated with parathyroid hyperfunction. Seven patients suffered pancreatitis associated with primary HPT and three with HPT after renal transplantation. We have also reviewed the world literature and have identified 107 cases reported from 1947 to 1985.

Patients and methods

We report 10 patients with pancreatitis and hyperparathyroidism. Hyperparathyroidism was diagnosed on the basis of surgical findings (eight instances) or persistent hypercalcaemia for which no other cause could be found (two instances, patients 8 and 9). There were six men and four women with ages ranging from 27 to 67 years. Eight patients had hypercalcaemia and two had hypocalcaemia after parathyroidectomy. A total of 7 patients were drawn from a series of 86 cases of primary hyperparathyroidism seen at the University of Barcelona from 1975 to 1985; 3 patients, who had hypercalcaemia and pancreatitis after renal transplantation, were drawn from a series of 236 kidney transplantations carried out at the University of Minnesota between April 1980 and April 1982.

Eight patients experienced acute pancreatitis and two chronic pancreatitis. Abdominal pain was the main complaint of pancreatic disease. Associated risk factors were present in five cases namely, total gastrectomy (one case), alcoholism (one case) and treatment with azathioprine and prednisone (three cases). A summary of this series is presented in *Table 1*.

Discussion

The first case report associating HPT with pancreatic lithiasis was published in 1947 by Martin and Canseco[2] although it was not until Cope and colleagues[3] had written their classic paper on the subject that pancreatitis began to be considered as another manifestation of primary HPT. Mixter *et al.*[4], from the same institution, reported 11 patients with inflammatory pancreatic disease drawn from a series of 155 cases of primary HPT, an incidence of 7 per cent, and were able to collect 51 cases from the literature. In 1966 Pyrah and Hodkinson[5] summarized the circumstances in which pancreatities had been found in association with parathyroid hyperfunction: (1) acute or acute recurrent pancreatitis that leads to the diagnosis of HPT and is cured by parathyroidectomy; (2) acute pancreatitis after parathyroidectomy; (3) acute pancreatitis occurring after non-parathyroid surgery in patients with HPT; (4) acute pancreatitis complicating parathyrotoxic crisis; (5) chronic relapsing calcifying pancreatitis and (6) 'tertiary' HPT complicating chronic pancreatitis with prolonged steatorrhoea and hypocalcaemia. During the same period other cases were reported[6,7] and the Mayo Clinic group found an incidence of 2·9 per cent in a series of 450 patients with HPT[8].

Reeves and Delbridge[9] reported that 9·3 per cent of their series of 86 patients undergoing parathyroidectomy for primary HPT developed abdominal symptoms associated with hyperamylasaemia. Although this high incidence of pancreatitis after parathyroidectomy has not been encountered in any other institution, it is a complication that can certainly happen, as evidenced by our patients 4 and 10.

In 1968 Terisse from the University of Lyon[10] carried out an extensive review of the subject, collecting 83 cases of pancreatitis associated with primary HPT. Some of his conclusions are worth noting: (1) this complication occurs predominantly in middle-aged men; (2) in about 16 per cent the cause of HPT was a parathyroid carcinoma and in these cases calcific pancreatitis was the most common type of pancreatitis, and (3) about 70 per cent of the patients suffered from acute relapsing or chronic pancreatitis and calcifications were seen in most of them.

Kelly[11] carried out an interesting experimental study with the aim of clarifying the pathogenesis of pancreatitis associated with hyperparathyroidism. In a model of endogenous HPT he was able to demonstrate that persistent hypercalcaemia would increase the calcium content of the pancreatic juice and lead to an accelerated 'intrapancreatic' conversion of trypsinogen to trypsin. This in turn would result in an insult to the pancreatic ducts and parenchyma. He could also show some relationship between the degree of hypercalcaemia and the severity of pancreatic lesions. This work corroborated previous findings by Haverback *et al.*[12].

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Table 1 *Summary of 10 patients with pancreatitis and hyperparathyroidism*

Case	Age	Sex	HPT*	Serum Ca (mmol/l)	Type of pancreatitis	Main symptom	Other symptoms	Risk factors	Outcome
1	33	M	P	3·5	Chronic calcifying	Pain, steatorrhoea	Bone disease, nephrocalcinosis	None	Good
2	69	M	P	3	Acute	Pain	Nephrolithiasis	None	Good
3	40	M	P	4·4	Acute persistent	Pain, ileus	Bone disease, nephrocalcinosis	None	Death
4	66	M	P	1·5†	Acute	Pain	Nephrolithiasis	None	Good
5	44	F	P	2·75	Acute	Pain	MEN 1	Total gastrectomy	Good
6	40	F	P	2·65	Chronic calcifying	Recurrent pain	D. ulcer, nephrolithiasis	None	Good
7	67	M	P	3·75	Chronic	Pain	None	Alcohol	Good
8	40	F	RT	3·42	Acute	Pain	None	Prednisone, azathioprine	Death
9	46	M	RT	3	Acute	Pain, abscess	None	Prednisone, azathioprine	Good
10	27	F	RT	1·6†	Acute	Ileus, abscess	Bone disease	Prednisone, azathioprine	Death

* P, primary hyperparathyroidism; RT, hyperparathyroidism after renal transplantation
† Post-parathyroidectomy

Table 2 *Clinical characteristics of 107 patients (mean age 50 years) with pancreatitis associated with primary hyperparathyroidism*

Characteristics	Percentage of patients
Sex	
Female	46·7
Male	53·3
Pancreatic symptoms	
Abdominal pain	67·3
Nausea and vomiting	100
Steatorrhoea	14
Weight loss	8
Bone disease	26·5
Other symptoms	
Nephrolithiasis	40
Nephrocalcinosis	14
Renal failure	8
Hypercalcaemic crisis	23·5
Metastatic calcifications	14·7
Gallstones	23·5
Alcohol abuse	10·3
Type of pancreatitis	
Acute	35·4
Acute relapsing	12·1
Chronic	37·4
Unknown	15
Parathyroid pathology	
Adenoma	67·3
Hyperplasia	10·3
Carcinoma	9·3
Unknown	13

In 1980 Bess and co-workers from the Mayo Clinic[1] reported that, in a large series of 1153 patients with proven primary HPT, only 17 were encountered with associated pancreatic inflammatory disease. These authors suggested that the alleged association between these two conditions was probably due to bias in patient selection or to chance alone. However, it is worth noting that, at their institution, many patients with asymptomatic hyperparathyroidism[13] and/or slight hypercalcaemia are submitted to parathyroid surgery. According to the works of Terisse[10] and of Kelly[11], this type of patient is less prone to develop pancreatitis than those exhibiting moderate to severe hypercalcaemia. On the other hand, a few cases have been reported in which hypercalcaemia not attributable to HPT has been implicated in the pathogenesis of acute pancreatitis. Hypercalcaemia during parenteral nutrition, or attributable to calcium infusion, myeloma, disseminated breast cancer or severe hyperthyroidism, have all been associated with pancreatitis[14–19]. This further supports the concept that hypercalcaemia *per se* may give rise to pancreatic inflammation and that although factors other than hypercalcaemia could lead to pancreatitis in patients with HPT (unrecognized gallstones, alcoholism or drugs) elevated serum calcium should not be considered to be unrelated to pancreatic symptoms.

The seven patients with pancreatitis and primary HPT reported herein have been drawn from a series of 86 patients with this endocrine disorder observed from 1975 to 1985, for a prevalence of 8 per cent, similar to the 7 per cent referred to by Mixter *et al.*[4] and by Coffey *et al.*[20]. In our series the association was again predominantly seen in men (60 per cent) as confirmed by our review of 107 published cases[9,10,21–30] (*Table 2*) in which men accounted for 53·3 per cent of the cases. This slight predominance of men is significant, as primary HPT is twice as common in women as in men. We also found that pain and vomiting were the most common manifestations of pancreatic disease. Calcifications were observed in 20 per cent of the cases and in two out of three patients with chronic pancreatitis. Renal symptoms were the most commonly associated complication of primary HPT. One-half of the patients had nephrolithiasis, 37 per cent had chronic renal failure and 25 per cent had polyuria and polydipsia. Bone disease was present in 26·5 per cent although we feel that the lack of information about bone involvement may give a falsely low figure. The advanced nature of HPT in our patients with pancreatitis is evidenced by the fact that some form of metabolic and/or radiographic bone disease was present in 70 per cent of them.

The three patients with pancreatitis and HPT after renal transplantation represent an interesting group. Pancreatitis is observed in 2–6 per cent of kidney transplant recipients and has been blamed on prednisone, pre-existing gallstones and hypercalcaemia[31–33]. Penn and colleagues[31] found that four out of twelve patients with acute pancreatitis after renal transplantation had hypercalcaemia ranging from 2·75 to 4·15 mmol/l. We showed that pancreatitis was a significant problem in a series of patients with hypercalcaemia equal to or over 3 mmol/l after renal transplantation[33]. In this study we compared 14 hypercalcaemic with 11 normocalcaemic patients with a functioning renal allograft, matched for age, sex, diabetes and immunosuppressive treatment. Two cases of acute pancreatitis were observed during follow-up in the hypercalcaemic group and none in the normocalcaemic controls. The possibility of hypercalcaemia being a causative or a predisposing factor should not be dismissed and parathyroidectomy should probably be carried out in renal transplant recipients showing persistent hypercalcaemia or hypercalcaemia equal to or over 3 mmol/l at any time during follow-up[33].

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Surgery in tropical pancreatitis

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Nineteen consecutive patients with tropical pancreatitis and chronic pancreatic pain operated upon over a 3-year period in Kerala, India, are reported. The pancreatic ductal morphology was studied by ultrasound scan, endoscopic retrograde cholangiopancreatography and/or operative pancreatography. In 17 patients, duct drainage by lateral pancreatojejunostomy and/or transduodenal pancreatic sphincteroplasty constituted the main surgical procedure. Caudal pancreatic resection was required in six of these patients. Unresectable pancreatic masses were found in two patients. Three patients died. Of the 16 survivors, 14 had good relief of pain within the limits of the available follow-up. In analysing the results, patients with 'obstructive pancreatitis' were found to have increased morbidity and mortality. The need to diagnose this subgroup of chronic pancreatitis pre-operatively is discussed.

Keywords: Tropical pancreatitis, ultrasound scanning, radiology

The southern Indian state of Kerala has the highest incidence of tropical pancreatitis in the world[1,2]. The onset of the disease is in adolescence or childhood, and alcohol is not an aetiological factor. Reports of the results of surgery are few[3–6] and the pancreatic ductal and parenchymal changes in this condition have not been described fully.

The study described here is the first series in which pancreatic imaging has been carried out pre-operatively in a group of patients thought clinically to have tropical pancreatitis. The morphological changes found at surgery are described and the results analysed according to the operative findings and histopathology.

Patients and methods

Over the 3-year period September 1983 to October 1986, 68 patients with a clinical diagnosis of tropical pancreatitis were seen in the gastroenterology clinic of the Deva Matha Hospital, Koothattukulam, India. Twenty-eight patients had intractable or frequent pancreatic pain, and nineteen of these underwent operation. These 19 patients form the basis of the present report. There were 13 male and 6 female patients ranging in age from 17 to 59 years; 15 of the patients were in the age group 25–50 years.

All 19 patients presented with pancreatic pain and 8 were insulin-dependent diabetics. The duration of pain was less than 1 year in six patients, 1–5 years in five patients, over 5 years in six and over 10 years in two patients. Clinical jaundice with elevation of serum alkaline phosphatase concentrations was seen in three patients.

Imaging techniques

Pancreatic calcification was seen on abdominal plain films in 17 patients. In the two patients with acalculous pancreatitis, ultrasound scan showed a dilated pancreatic duct. Mass lesions picked up on ultrasound scanning were one cyst (related to the head of the pancreas) and two abscesses (related to the tail), all of which contained stones. The ultrasound scan was reported as normal in one patient who proved at surgery to have a mass in the body of the pancreas. Common bile duct obstruction was demonstrated on ultrasonography in the three patients with jaundice.

Endoscopic retrograde cholangiopancreatography (ERCP) was attempted in all 19 patients, and was successful in 15. It demonstrated gross dilatation of the pancreatic duct in 11 patients (*Figure 1*); in 3 the proximal duct was dilated but in the caudal region it was shrunken (*Figure 2*), and in one patient the pancreatic duct ended abruptly in the head. In four patients the duct was not delineated; three of these patients proved to have a duct choked with stones and in one it was occluded by a neoplasm. Three patients had the congenital anomaly of pancreas divisum.

Operative pancreatography was done in six cases: it successfully demonstrated a dilated pancreatic duct in two of the three cases in which calculous obstruction had caused failure of ERCP. In the third patient, an operative pancreatogram could not be achieved because of marked atrophy of the pancreas. Operative pancreatography was also useful in demonstrating a ductal stricture in the head of the pancreas not clearly seen on ERCP, and in one patient in demonstrating the appearance of duct occlusion by neoplasm.

Operative findings and procedures

On gross appearance and histopathological findings our patients could be divided into three groups:

Group 1: Fibrotic pancreas. This was found in 15 patients. Biopsies showed typical features of chronic pancreatitis. Cysts were found in four cases and one had an abscess in the tail of the gland. One of these patients also had common bile duct obstruction.

All of this group of patients underwent pancreatic duct drainage. One had transduodenal pancreatic sphincteroplasty alone, and 14 underwent pancreatojejunostomy. Three of these patients were found to have cysts of the head and body of the pancreas which were drained together with the dilated pancreatic duct. Five patients required

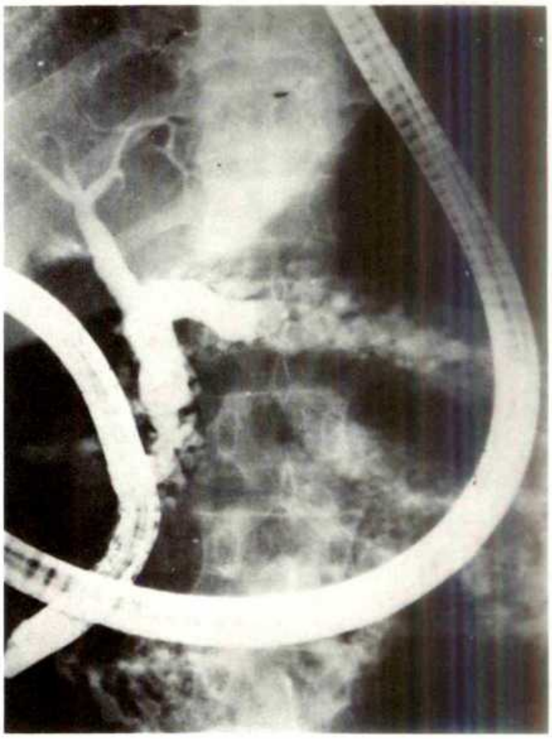

Figure 1 *ERCP of a 36-year-old man showing dilated pancreatic ductal system with multiple filling defects in the main duct due to calculi (Group 1)*

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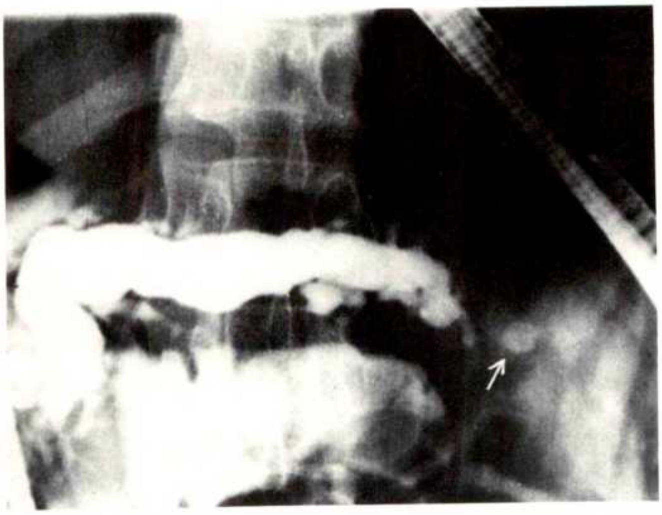

Figure 2 *ERCP of a 28-year-old man showing dilated pancreatic duct blocked at the junction of body and tail. Stones are present distal to the block (arrow). This patient required caudal resection for an abscess 2 months after pancreatojejunostomy (Group 1)*

concomitant caudal resection: three of these patients had a shrunken pancreatic duct in the tail, one had a caudal abscess and one had multiple cysts of the side branches in the tail of the pancreas (*Figure 3*). Common bile duct obstruction in one patient was relieved by transduodenal sphincteroplasty.

Removal of pancreatic stones was often time consuming and difficult. In 5 of the 15 patients in this group, stones in the side branches were too numerous to be removed. In one patient, residual calculi in the tail resulted in a pancreatic abscess which became manifest 2 months after surgery, necessitating re-exploration and caudal resection.

There was a marked increase in peripancreatic fat in five patients, which made the anastomosis technically difficult.

Group 2: Soft, oedematous pancreas. This was seen in two patients, both of whom had a localized obstruction to the proximal pancreatic duct on ERCP. Both underwent lateral pancreatojejunostomy; one also required choledochoduodenostomy for common bile duct obstruction. Locating the pancreatic duct in these patients was difficult because of parenchymal swelling. Biopsy in both cases showed evidence of acute pancreatitis.

Group 3: Neoplasm of the pancreas. Two patients had unresectable pancreatic masses associated with intraductal calcification. In one the mass was causing common bile duct obstruction and choledochojejunostomy was done. Both masses were biopsied using a Trucut needle and the histopathology was reported as chronic pancreatitis in both cases. Despite this, the appearance at operation led to pancreatic carcinoma being adopted as the working diagnosis.

Results

Morbidity and mortality

Group 1. One patient died 12h after surgery owing to respiratory failure. She had presented with a pancreatic abscess that did not resolve with antibiotic therapy, and was taken for surgery in a moribund condition. Two patients required re-exploration 2 and 6 months after longitudinal pancreatojejunostomy for caudal pancreatic abscess and jejunal obstruction respectively. Of the 14 survivors, 13 are free of pain, have gained weight, and 10 are back at their jobs. The patient with severely atrophic pancreas who underwent transduodenal sphincteroplasty alone has been placed on long-term enzyme supplements and cimetidine to minimize steatorrhoea after operation.

Group 2. The postoperative period was stormy in both of these patients: both developed pancreatic fistulae and intra-abdominal sepsis. One required re-exploration and 80 per cent left-to-right pancreatectomy for secondary haemorrhage from the suture line. The bleeding was controlled, but the patient succumbed to intra-abdominal sepsis 45 days after surgery.

The other patient's fistula subsided on conservative treatment. He is well 18 months after surgery, but has a large incisional hernia.

Group 3. These two patients showed steady deterioration postoperatively; one developed a small-bowel fistula and died of renal failure on the 33rd postoperative day; the other patient has developed supraclavicular lymph node enlargement 6 months after surgery. Lymph node biopsy confirmed the presence of metastasis from adenocarcinoma of the pancreas.

Overall results

The three deaths give an overall perioperative mortality of 16 per cent in this series of patients. Of 16 survivors, one now has confirmed adenocarcinoma rather than tropical pancreatitis alone and will not be considered further. Of the remaining 15 patients, 13 can be regarded as having had a 'good' result in that they survived surgery without major complications and are pain free on current follow-up.

Discussion

Tropical pancreatitis is a form of chronic pancreatitis which is seen in Asia, Africa and South America in young adults and children, and which is characterized by a high incidence of diabetes mellitus, disseminated intraductal calcification of the pancreas and recurrent abdominal pain. It was first reported from Indonesia in 1959 and has subsequently been found to occur in India, Ceylon, Uganda, Nigeria, Malawi, Congo, Zaire and Brazil[7]. The highest incidence of 50 cases per 1000 population is reported from the southern Indian State of Kerala[2].

The aetiology of tropical pancreatitis is unknown, although it is well recognized that biliary tract disease and alcoholism are not primarily responsible. The popular theory that protein-calorie malnutrition is responsible is based on the fact that these patients usually come from a poor socio-economic background[7-9]. Clustering of cases in families is well known but no definite genetic pattern of transmission has been established. The role of dietary toxins, particularly the cyanogenetic glycosides contained in the popular tuber cassava (*Manihot esculenta*), is being investigated. Mucoviscidosis is not associated with this syndrome, and viral infection (although common in these patients) probably has no causal relationship[2,7].

Chemically, the pancreatic stones are composed almost

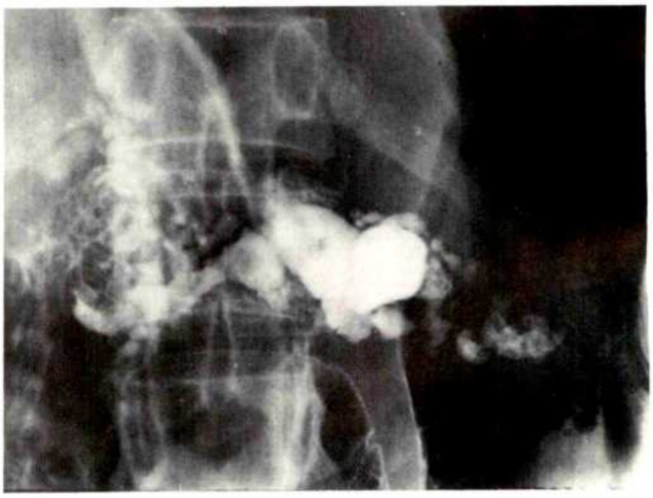

Figure 3 *ERCP of a 39-year-old woman showing cystic dilatation of the pancreatic duct and side branches in the tail, with calculi distal to the point where the duct ends. Caudal resection was performed together with longitudinal pancreatojejunostomy (Group 1)*

entirely of calcium carbonate[2]. Normal pancreatic juice is always supersaturated with calcium carbonate and factors that prevent its precipitation are being evaluated. Pancreatic stone protein appears to be one important factor, and the pancreatic juice in patients with chronic pancreatitis is deficient in this protein[2].

Patients usually present with diabetes mellitus and/or abdominal pain and the diagnosis is made by abdominal radiograph. Steatorrhoea is rare, probably because of the low levels of fat in the diet commonly consumed. Exocrine deficiency manifests clinically as weight loss[7]. Serum amylase levels are characteristically normal or low[7,9]. Management consists of controlling the diabetes, which is usually brittle with hypoglycaemic episodes being common. Ketosis occurs in 20 per cent of patients[7], and vascular complications are common. The age at death in the first 400 cases reported from Kerala was between 20 and 30 years[1].

Management of the pain is difficult. Enzyme supplements and anticholinergic drugs are commonly used, but in 30 per cent of patients pain is intractable and severe enough to warrant surgery. Other indications for surgery are common bile duct obstruction and pseudocyst formation. Imaging of the pancreas has not been carried out routinely in patients with tropical pancreatitis. Dilated pancreatic ducts were demonstrated by ERCP by Balakrishnan *et al.* in 1985[10], but the results of treatment in their cases is not known. We have found that ultrasound scan and ERCP are invaluable in the assessment of patients who might be candidates for surgery.

The Marseilles classification of 1962 provided the basis for improved understanding of pancreatitis throughout the world. Recognition of the need to correlate structural and histopathological abnormalities of the pancreas with the clinical presentation has resulted in the Cambridge classification of 1983 and the updated Marseilles classification of 1984[2,11]. We have found that the classification proposed by Sarles, which recognizes subgroups of patients with chronic pancreatitis in whom exocrine function is relatively well preserved, is of greater therapeutic value[2].

Our patients with histopathological changes typical of chronic pancreatitis (Group 1) withstood surgery with minimal morbidity and mortality. Pre-operatively these patients can be recognized by the fact that the pancreatic duct is widely dilated, and that stricturing and calculus formation are distributed throughout the length of the pancreas. Diabetes mellitus and weight loss due to exocrine deficiency are marked. When adequate drainage could be established, the relief of pain and consequent nutritional improvement were dramatic. In patients with recurrence of pain the fault probably lay with surgical technique. The only death in this group was the patient with a pancreatic abscess.

Our patients in Group 2 come into the category of obstructive pancreatitis as classified by Sarles[2]. Ductal dilatation was caused by a localized obstruction at the head of the pancreas. Endocrine and exocrine pancreatic function were well preserved. The gland was oedematous and active inflammation of the pancreas was seen on histopathology. The morbidity and mortality after pancreatojejunostomy were high. Awareness that such a subgroup exists, and the use of CT scanning to image the pancreatic parenchyma in patients with localized proximal duct obstruction, would help in the pre-operative identification of these patients.

Neoplasms of the pancreas were thought to be present at surgery in our patients in Group 3. Both had calculi. One presented with obstruction to the duodenum and common bile duct due to a mass in the head of the pancreas, and died 1 month after choledochojejunostomy. Histopathological proof of malignancy is not available for this patient. In the other patient who presented with pain and had a mass in the body of the pancreas, histopathological proof of malignancy was found only 6 months after surgery when she developed supraclavicular lymph node metastases. A CT scan done at this time showed that the pancreatic mass had increased in size. There were no liver or lung metastases and other abdominal organs were normal. The occurrence of pancreatic cancer in cases of tropical pancreatitis is well documented[5,7-9,12]. Histopathological proof may be difficult to obtain in these cases at the primary operation, and the diagnosis may have to rest on the radiological demonstration of a blocked pancreatic duct in the presence of a mass that does not resolve into either a cyst or an abscess on follow-up.

The debate continues as to whether resection or drainage constitutes the ideal surgical management in chronic pancreatitis[13-16]. The uncontroversial fact is that treatment must be individually tailored in each case[16] A few guidelines for a surgeon confronted with a case of tropical pancreatitis are as follows:

1. The patients are usually young and over 70 per cent have dilated ducts: drainage by longitudinal pancreatojejunostomy is therefore the primary procedure of choice.
2. The ideal length of the anastomosis cannot be stated in centimetres. An ideal drainage is one in which the Roux loop of jejunum is juxtaposed to the anterior surface of the pancreas in such a way that pancreatic secretion from every part of the gland can flow, not prograde or retrograde, but sideways—throughout its length—into the jejunum. This ideal is almost always possible in the body of the pancreas, but in the head and tail it is often difficult to achieve Sometimes the tail is hopelessly diseased, with the main pancreatic duct narrowed by the surrounding fibrotic process, or the side branches become hugely dilated and even cystic. In such circumstances a caudal resection may be combined with longitudinal pancreatojejunostomy: this was required in six of our patients. In the head of the pancreas the duct dips posteriorly and the thickness of pancreatic tissue anterior to the duct increases. Dividing this often results in troublesome haemorrhage and, even though this can usually be controlled, the duct is then located so deeply that mucosa-to-mucosa anastomosis may be difficult. Draining the main duct in the head of the pancreas may be possible by combining a transduodenal sphincteroplasty with the longitudinal pancreatojejunostomy.
3. Technical difficulties include increased peripancreatic adipose tissue that makes it difficult to suture the jejunum to the pancreatic capsule. We have made it standard practice to do a two-layer anastomosis using interrupted silk sutures on the outside, and a continuous polyglycolic acid suture for the inner mucosa-to-mucosa layer. The other common technical problem is the difficulty of achieving complete clearance of stones. This is the most time-consuming part of the operation and it is often impossible to clear the stones from the side branches in the head of the pancreas. Incomplete removal of stones has resulted in a caudal pancreatic abscess 2 months postoperatively in one of our patients. A similar problem may also be encountered in the head of the pancreas, but has not occurred in our series. The only solution to this problem, namely a Whipple resection, may represent a difficult decision in a young patient whose side branch calculi in the head may remain asymptomatic if the main pancreatic duct is adequately drained, and may even disappear with time[3,4].

In concluding, we wish to stress the importance of recording the ductal and parenchymal abnormalities of the pancreas by suitable imaging techniques in every case of tropical pancreatitis coming to surgery. This is the only way of individualizing the operative procedure for a given patient, and it remains a fixed point of reference for evaluating the patients postoperatively and for comparing the results of different workers.

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Announcement

Abbreviations, a curse

Sir

At international meetings I and colleagues from the continent of Europe have noticed an alarming and increasing incidence of CUA among British doctors. CUA is so common that it is lowering the value of many UK contributions to international gatherings. Were it not for CUA, presentations from the UK would be among the best at most meetings, making the conference well worth attending; the quality of the research and clinical skills presented are usually high. What is needed is a campaign to prevent CUA among my British colleagues so that phrases such as 'Hopefully BAL will provide more information about the role of ECP and NCF in patients with COPD' will no longer be heard at meetings attended by doctors from the rest of Europe. Those of us for whom English is not our native tongue may find it difficult not to lose the thread while trying to work out what various abbreviations (and slang phrases) mean. By the way, did I forget to say that CUA means Confusing Unnecessary Abbreviations?

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Pancreatic trauma: acute and late manifestations

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A retrospective analysis of 47 patients with pancreatic trauma is presented. A total of 43 patients presented with acute pancreatic injury, 32 after blunt abdominal trauma. Isolated blunt pancreatic injuries were a considerable diagnostic problem with a mean delay from trauma to operation of 9·4 days. At operation peripancreatic drainage in mild injuries and distal resection in cases of ductal injury were the commonest procedures. The overall mortality was 19 per cent, but only three of the eight deaths were attributable to the pancreatic injury. The overall complication rate was 63 per cent and the pancreatic complication rate was 33 per cent. Four patients presented with chronic pancreatitis resulting from previously untreated blunt abdominal trauma 0·5–21 years earlier. Clinically, they did not differ from the manifestations of chronic pancreatitis of other aetiological origins.

Keywords: Abdominal injuries, pancreas injuries, chronic pancreatitis

Pancreatic injuries occur in 0·2–6 per cent of cases of abdominal trauma[1–5]. Associated injuries are common and mainly responsible for the high mortality rate of 13·8–31 per cent[6–15]. Blunt pancreatic injury may be isolated presenting considerable diagnostic problems[16,17]. It may remain undiagnosed at laparotomy and 'heal' spontaneously, leading to chronic pancreatitis with its late manifestations[18–20].

The present report reviews the wide spectrum of pancreatic injuries with special reference to acute and late complications.

Patients

The hospital records of 47 patients treated operatively for pancreatic injury in the 19-year period between 1967 and 1985 were reviewed retrospectively. Forty-three patients presented with acute abdominal trauma, representing 5 per cent of the total patients with abdominal trauma treated during the same period. Four patients, initially untreated for pancreatic injury, presented with its late manifestations as chronic pancreatitis

Acute presentation

Of the 43 patients with acute pancreatic injury, 37 were males and the mean age was 32 years (range 16–62). Penetrating abdominal injury was present in 11 patients (7 stabs, 4 gunshot wounds); 5 of them arrived in shock, defined as a systolic blood pressure less than 90 mmHg. They all had a laparotomy after initial evaluation and resuscitation. The delay between trauma and operation varied from 1 to 16·5 hours (mean 3·3 hours). Two patients with blunt abdominal trauma and clinical shock due to intra-abdominal haemorrhage were operated on without further diagnostic procedures. The remaining 30 patients (70 per cent) with blunt abdominal trauma, of which a road traffic accident was the commonest cause (75 per cent of all blunt injuries), were subjected to further diagnostic studies including serum and urine amylase determinations and radiological investigations. Ultrasonography or computed tomography were not routinely used in the assessment of abdominal trauma patients. In isolated blunt pancreatic injuries the delay between the trauma and the operation varied from 1 to 26 days, mean 9·4 days.

Late presentation

Four patients, three men and one woman, presented with chronic pancreatitis due to earlier blunt abdominal trauma (two from road traffic accidents and two from a blow to the abdomen). The mean age was 27 years (range 21–37) at the time of the injury. The delay from trauma to the first symptoms was 0 5, 4, 11 and 21 years. The criteria for determining that previous abdominal trauma was the cause of pancreatic injury were:

1. clear history of blunt abdominal trauma
2. no other aetiological factors of pancreatic disease
3. no history of pancreatic disease before the injury
4. no discrepancy between the operative finding and the history of the abdominal trauma.

The diagnosis of chronic pancreatitis was based pre-operatively on ultrasonography, computed tomography and endoscopic retrograde pancreaticography and was also verified at operation.

Classification of pancreatic injuries

On the basis of their location and severity, pancreatic injuries were classified into four categories according to Lucas[21].

I Simple superficial confusions with minimal parenchymal damage. Any portion of the pancreas can be affected but there is no question of disruption of the pancreatic duct
II Deep lacerations, perforations or transection of the tail or the body of the pancreas with the possibility of pancreatic duct injury
III Severe transection, perforation or crushing injuries to the head of the pancreas with or without ductal injury, but with an intact duodenum
IV Combined pancreaticoduodenal injuries. These are further classified as combined injuries with mild pancreatic injury and severe damage of the pancreas with ductal disruption.

Results

Type of injury

Acute pancreatic injury. The locations of the pancreatic injuries are shown in *Table 1*. There were 21 grade I, 15 grade II, 4 grade III and 3 grade IV injuries. Nine patients had pancreatic trauma without lesions to any other organs. The remaining 34 patients had a total of 111 associated injuries predominantly involving liver 18, mesentery 13, and thorax 12.

Late pancreatic injury. Of the four patients who presented with chronic pancreatitis, a pancreatic pseudocyst was seen in three patients. The fourth patient had a mid-pancreatic transection with pancreatic abscess. In each case the proximal part of the pancreas was normal.

Operations

Acute pancreatic injury. The methods of treatment and the associated mortality and morbidity are summarized in *Table 2*.

Table 1 *The site of pancreatic injury in blunt and penetrating pancreatic trauma*

	The site of pancreatic injury			
Trauma mechanism	Head	Body	Tail	Total
Blunt	12	15	5	32
Gunshot	2	1	1	4
Stab	3	4	0	7
Total	17	20	6	43

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Table 2 *Method of treatment with associated pancreatic complication and mortality rates*

Method of treatment	Grade of pancreatic injury I	II	III	IV	No. of patients with pancreatic complications	No. of pancreatic deaths
Drainage	12	4	1		4*	
Drainage and suture	7				4	1
Suture only	1				0	
Roux-Y anastomosis		1	1		1	
Distal resection		9	2†		2	
Pancreaticoduodenectomy				3	2	1
Missed pancreatic injury	1				1	1
Died on the table		1‡			0	
Total	21	15	4	3	14	3

* All 4 complications in grade II–III injuries; † Includes one near-to-total resection; ‡ Due to exsanguination from a liver injury

Table 3 *Pancreatic complications in 14 patients after acute pancreatic injury*

Complication	No of complications
Pancreatic fistula	5
Pancreatitis	5
Pseudocyst	2
Leakage of pancreatic/biliary anastomosis after pancreaticoduodenectomy	2
Total	14

The majority of grade I pancreatic injuries were treated by simple peripancreatic sump drainage and suture repair of the pancreatic tear. In grade II and III injuries distal resection was the most common procedure. One patient with grade II injury (transection) was treated with a Roux-en-Y anastomosis to the distal pancreas and closure of the proximal stump, and one patient with partial laceration of the head of the pancreas was treated with Roux-en-Y anastomosis to the injury. All three pancreaticoduodenal injuries were managed with pancreaticoduodenectomy (Whipple procedure). The end-to-end pancreaticojejunostomy was performed in two layers by invaginating the remaining gland into an open limb of gut. The end-to-side choledochojejunostomy was carried out over the long arm of a T tube. In all three cases antecolic gastrojejunostomy and cholecystectomy completed the procedure.

Late pancreatic injuries. All four patients were treated with distal resection without any complications.

Mortality

Eight patients operated on for acute pancreatic injury died. The mortality rate was 19 per cent. Five of the deaths followed blunt and three penetrating abdominal injuries. Three of the deaths were attributable to the pancreatic injury. Two patients died due to haemorrhagic pancreatitis, one after grade I injury treated with drainage, 5 days postoperatively. The other patient was initially treated in another hospital for multiple injuries and the pancreatic injury to the tail was not recognized at the initial laparotomy. A haemorrhagic pancreatitis developed and the patient died after multiple complications 89 days after the injury. The third pancreatic death was due to rupture of all anastomoses after pancreaticoduodenectomy with subsequent sepsis, multiple organ failure and death 55 days after injury.

The other five causes of death were: haemorrhage from a liver injury, haemorrhage from a kidney injury, hepatic failure after liver injury (two cases) and renal failure following kidney injury.

There were no deaths following isolated pancreatic injuries. In patients with associated injuries the mortality rate was 24 per cent. The mortality rate in patients with proximal pancreatic injuries (head, body) was 19 per cent and in distal injuries (tail) 17 per cent.

Table 4 *The causes of pancreatic complications after acute pancreatic trauma*

Cause	No. of patients (no. of pancreatic deaths)
Missed ductal injury	4
Postoperative pancreatitis or pseudocyst of unknown cause	4 (1)
Anastomotic leakage after pancreaticoduodenectomy	2 (1)
Insufficient distal resection	1
Incomplete pancreatic haemostasis	1
Long patient delay*	1
Missed pancreatic injury	1 (1)
Total	14 (3)

* Lesser sac abscess present at primary operation

Morbidity

Sixteen patients operated on for acute pancreatic injury survived without complications. The remaining 19 surviving patients had a total of 36 complications. The overall complication rate was 63 per cent and the pancreatic complication rate was 33 per cent (*Table 3*). In isolated pancreatic injuries the complication rate was 67 per cent and in patients with associated injuries 62 per cent. The complication rate in proximal pancreatic injuries was 62 per cent and in distal 67 per cent. (Complication rate = (number of non-survivors + number of survivors with complications)/total number of patients.)

In the patients with grade II–III pancreatic injuries the pancreatic complication rate in those treated with distal resection was 18 per cent (two fistulas) and 80 per cent in those treated with drainage only (three fistulas, one pseudocyst).

Overall, there were 14 patients with pancreatic complications. The underlying causes are summarized in *Table 4*.

The average hospital stay among survivors was 35 days, range 6–125 days.

Discussion

The number of pancreatic injuries due to blunt abdominal trauma (74 per cent) is high when compared with previously published material[6–14]. The explanation may be the relatively low incidence of gunshot wounds in Finland. Our material does not give a true figure about the actual incidence of pancreatic injuries (5 per cent of all abdominal injuries), since most multitrauma patients, and all patients with head injuries, are treated in another centre.

The mean delay from trauma to operation of 3·3 hours in penetrating pancreatic injuries is acceptable and since our policy has been to explore all penetrating abdominal injuries, the longer delays are caused by late presentation.

In blunt pancreatic injuries, the signs of intra-abdominal haemorrhage from associated injuries or of peritonitis after rupture of a hollow viscus usually lead to early operation with detection of the pancreatic injury. In isolated pancreatic injuries the pre-operative diagnosis is difficult and leads to long delays or even to a missed diagnosis of the pancreatic trauma.

Serum amylase determination is not a reliable indicator of the presence of a pancreatic injury[22] and our data of hyperamylasaemia in only 62 per cent of the 13 patients checked for amylase levels confirms this.

Peritoneal lavage, especially in unconscious patients, is accurate in detecting intraperitoneal organ injury, but in isolated retroperitoneal pancreatic trauma the procedure often gives false-negative results, although amylase determination from the peritoneal fluid may help to detect isolated pancreaticoduodenal injuries[19].

Computed tomography may be normal in acute pancreatic injuries, but it is valuable in the observation period and in detecting complications after pancreatic trauma[17,23]. Ultrasonography and endoscopic pancreatography are useful in the management of late manifestations of missed pancreatic trauma[18].

The present report confirms the possibility that an isolated pancreatic injury, even complete transection of the pancreas, may remain undiagnosed and 'heal' spontaneously, later leading to chronic pancreatitis and its complications. Clinically, such injuries do not differ from the manifestations of chronic pancreatitis of other aetiological origins.

Recognition of the pancreatic injury at the time of initial surgical exploration, identification of the possible ductal injury and institution of adequate surgical drainage are the cornerstones of successful treatment of all pancreatic injuries[14]. Controversy exists regarding distal resection *versus* drainage in the treatment of distal pancreatic injuries with ductal involvement[15]. Although the present material is limited the results confirm the lesser incidence of pancreatic complications after distal resection in the treatment of grade II pancreatic injuries compared with the group treated with drainage only. The importance of recognizing the ductal injury and of adequate and careful operative technique must be emphasized.

Pancreaticoduodenectomy may be indicated in 2–3 per cent of cases of pancreatic injury[14] and in 10 per cent of combined pancreaticoduodenal injuries[24]. The mortality rate varies from 24 to 40 per cent and most series show a high risk for complications[6,14,25]. Good results have been achieved by applying strict criteria for pancreaticoduodenectomy[26] and individualized treatment of combined pancreaticoduodenal injuries has been indicated[27].

Where pancreaticoduodenectomy is necessary, technical problems in the reconstruction of pancreatic and biliary anastomoses may arise due to the small size of the ducts. Because the duct is small in the normal pancreas and mucosa-to-mucosa anastomosis is difficult, invagination of the head of the gland into an open limb of gut has been suggested[7]. In most cases, the biliary-enteric continuity has been restored by an end-to-side choledochojejunostomy over a T tube[25,28]. If the small size of the common bile duct precludes a safe choledochojejunal anastomosis, a side-to-side cholecystojejunostomy with ligation of the common bile duct has been used as an alternative[28]. Because reflux of the jejunal contents in the biliary tree predisposes to stones, the gallbladder should not be preserved if a choledochojejunostomy is performed[26].

The overall mortality rate of 19 per cent compares well with other published series[6–15]. One of the three pancreatic deaths could probably have been avoided if the pancreatic injury had not been missed.

The incidence of pancreatic complications varies between 8 and 33 per cent[10,12,14,15]. In all, 14 of the 43 patients (33 per cent) in our series had pancreatic complications; half of these could have been avoided, e.g. the four patients with missed ductal injury, one incomplete distal resection, one inadequate pancreatic haemostasis and one missed pancreatic injury (*Table 4*).

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Staphylococcus epidermidis as a cause of postoperative wound infection after cardiac surgery: assessment of pathogenicity by a wound-scoring method

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Wound infection after clean surgery prolongs hospital stay but the organism most commonly isolated from wound discharge, Staphylococcus epidermidis, *is often dismissed as a contaminant or commensal. The wounds of 517 patients were assessed, after cardiac surgery, by a wound-scoring method ('ASEPSIS') and a close comparison was made of the appearance and clinical outcome of 89 wounds, from which bacteria were isolated. There was no significant difference in the scores of 49 wounds, where* S. epidermidis *was the sole isolate (9·5 per cent of all wounds, 95 per cent CI 6·9–12·0 per cent), and 13 wounds infected with* Staphylococcus aureus *(2·5 per cent, 95 per cent CI 1·2–3·9 per cent). Repeat cultures were obtained from 21 of the 49 wounds and, in 16 of these, the second isolate showed the same biochemical reactions and antibiotic resistance pattern as the first. Infection of sternal wounds is commoner with coagulase-negative staphylococci than with* S. aureus *and, clinically, is just as severe.*

Keywords: Heart surgery, wound infection, *Staphylococcus epidermidis*

Surgeons are familiar with the problem of an obvious, severe wound infection with wound separation, surrounding erythema and a purulent exudate, yet microbiology laboratory reports of 'no significant growth' or 'skin commensals only'. Further enquiry may reveal that *Staphylococcus epidermidis* has been grown but that its clinical importance is doubted. Severe sternal wound infection is an uncommon but serious cause of morbidity after cardiac surgery, occurring in 0·5–4·5 per cent of cases[1], while minor infection prolongs hospital stay and delays rehabilitation. Reports which assume that coagulase-negative staphylococci are not pathogenic in this context[2], deprive the clinician of guidance in a logical choice of therapy.

A prospective study of 517 cardiac surgical patients has provided the opportunity to assess the clinical appearance and bacteriological flora of all wounds that do not heal perfectly[3], and to establish whether *S. epidermidis* should be regarded as a pathogen in wound infection.

Patients and methods

Clinical methods

All patients undergoing cardiac surgery involving cardiopulmonary bypass were considered for study. Exclusion criteria were age less than 18 years, pregnancy, a history of allergy to penicillin or vancomycin, serum creatinine over 150 μmol/l, active infection or antibiotic treatment within the last 7 days.

All patients bathed with chlorhexidine soap solution (4 per cent chlorhexidine gluconate in a detergent base) before operation and, in theatre, the operation sites were prepared with a povidone iodine solution in alcohol All patients received antibiotic prophylaxis with teicoplanin or flucloxacillin and tobramycin.

Assessment of wound infection was made by a comprehensive scoring method (ASEPSIS), which has been published[3], but is summarized here (*Table 1* and *2*) On 5 of the first 7 days, all sternal and leg incisions were examined methodically by a single observer (A.P.R.W.), for wound separation, serous or purulent exudate, or erythema extending 5 mm or more from the line of the incision. The proportion of the wound, as measured to the nearest 10 per cent of its length, showing any of these features, was assigned a numerical score as set out in *Table 1*. After 1 week, five such scores had been recorded, each with a numerical value between zero (normal healing) and a possible maximum of 30, representing complete dehiscence of the wound with pus, serous exudate and erythema throughout its length

Other events contribute to the total score for up to 2 months, which was when the patients were reviewed (*Table 2*). Any bacterial growth from wound discharge increased the wound score by 10 points. Wound drainage in the ward by probing or aspiration added 5 points while surgical drainage or débridement under general anaesthesia added 10 points. Antibiotic treatment merited 10 points and prolongation of hospital stay beyond 14 days (or readmission) scored a further 5 points.

The total scores were grouped into five descriptive classes (*Table 2*) and compared for each bacterial species isolated by the χ^2 test with Yates's correction. Individual scores were also compared by the Mann–Whitney test[4,5]. Fisher's exact test was used to compare the frequencies of the measures of clinical significance for wounds infected with each organism. All tests were two-tailed. Confidence intervals (95 per cent CI) were estimated for proportions[5].

Laboratory methods

Swabs were taken from all discharging wounds and any bacterial growth after 48 h was identified by standard methods. Sensitivities to 12 antibiotics were performed by a modified Stokes' method. Methicillin resistance in coagulase-negative staphylococci was tested by incubation at 30°C. Resistance to novobiocin was also tested to identify *Staphylococcus saprophyticus*.

The species was identified biochemically by use of the API-Staph system, in accordance with the scheme of Kloos and Schleifer[6] Strains were differentiated by colonial morphology, pigmentation and

Table 1 *Points scale for the daily wound inspection*

Wound characteristic	Proportion of wound affected					
	0%	<20%	20–39%	40–59%	60–79%	>80%
Serous exudate	0	1	2	3	4	5
Erythema	0	1	2	3	4	5
Purulent exudate	0	2	4	6	8	10
Separation of deep tissues	0	2	4	6	8	10

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Table 2 *The wound score· ASEPSIS*

Criterion		Points
A	Additional treatment	
	Antibiotics	10
	Drainage of wound (general anaesthesia)	5
	Débridement of wound (general anaesthesia)	10
S	Serous discharge	daily 0– 5
E	Erythema	daily 0– 5
P	Purulent exudate	daily 0–10
S	Separation of deep tissues	daily 0–10
I	Isolation of bacteria	10
S	Stay as in-patient prolonged over 14 days	5
Total score (indicating category of infection)		
0–10	Satisfactory healing	
11–20	Disturbance of healing	
21–30	Minor wound infection	
31–40	Moderate wound infection	
>40	Severe wound infection	

Table 3 *Median sternal wound scores for each bacterial species isolated*

		Median wound score* (and quartiles)		
Organism	Number of wounds ($n=89$)	Clinical appearance (a)	Clinical consequences (b)	Total (a+b+10)
Pure/predominant growth				
Staphylococcus epidermidis	49	7 (4, 12)	0 (0, 5)	18 (14, 24·5)
Staphylococcus aureus	13	5 (1, 9·5)	0 (0, 20)	17 (11, 36·5)
Other staphylococci	4	7·5	0	17·5
Mixed growth (mainly Gram-negative spp.)	23	3 (1, 8)	0 (0, 5)	17 (11, 22)

* The wound score is expressed in three ways: (a) the sum of points for the clinical appearance of the wound in the first postoperative week; (b) the score for the clinical consequences of infection; (c) when a positive culture is obtained, ten points are added to (a)+(b) to complete the 'ASEPSIS' score

haemolytic activity[7]. Comparison of isolates by these methods and the antibiogram suggested which strains might be repeatedly isolated from wounds in which more than one swab was taken.

Four strains indistinguishable by these methods were sent to the Staphylococcal Reference Laboratory at Colindale for bacteriophage typing, as they were all associated with severe mediastinal infections.

Results

Between October 1984 and September 1986, 690 patients were considered for study but 121 were excluded by the selection criteria, and 52 others were withdrawn because they did not receive the antibiotic regimen as prescribed. Of the 517 patients remaining, 363 underwent coronary artery bypass surgery and the rest valvular or other intracardiac surgery. Severe sternal wound infection (a score over 40 by the ASEPSIS method), was recorded in 9 cases (1·7 per cent), and a moderate infection (31–40 points) in a further 5 (1·0 per cent). Minor wound problems (21–30 points), noted in 24 patients, would not necessarily be included in conventional reports of wound infection[3]. Another 61 patients (11·8 per cent) had some disturbance of healing. Bacteria were isolated from 89 wounds with serous or purulent discharge (17·2 per cent, 95 per cent CI 14·0–20·4 per cent). There were no severe leg wound infections and only two moderate and six minor category infections so that statistical analysis was not attempted.

Staphylococcus aureus was isolated from two minor and three severe sternal wound infections and eight sternal wounds with disturbance of healing, a total of 13 wounds (2·5 per cent, 95 per cent CI 1·2–3·9 per cent). However, coagulase-negative staphylococci were also isolated from eight of these wounds and Gram-negative bacteria in four cases. *S. epidermidis* was the sole isolate from 49 discharging sternal wounds (9·5 per cent, 95 per cent CI 6·9–12·0 per cent), 5 with severe infection, 4 moderate and 11 minor infections and 26 others with disturbance of healing. *S. epidermidis* was also isolated from three of eight sternal wounds which showed no abnormality at 1 week but broke down subsequently. Strains of *S. epidermidis* resistant to methicillin were isolated from 7/49 wounds.

The proportion of wounds with obvious infection (score ≥ 20) was similar for both species ($\chi^2=0·03$, $0·9>P>0·8$). Furthermore, the distribution of the individual wound scores (or the points for the daily clinical appearance) were not significantly different from those in which coagulase-positive staphylococci were isolated ($P>0·10$ by Mann–Whitney U test) (*Table 3*). More detailed investigation shows that the decision to drain or surgically débride a wound was more common in the presence of *S. aureus* (*Table 4*).

Repeated wound swabs had been taken from 21 of the 49 wounds in which *S. epidermidis* was the only isolate: in 16 of these, the strain isolated from the second sample had the same antibiotic sensitivities and biochemical profile as that in the first. Furthermore, one particular strain was associated with sternal sepsis in three different patients. All three isolates were resistant to penicillin, erythromycin, fusidic acid and trimethoprim and showed an identical profile on the API-Staph system (6706112). The isolates were not typable by the standard range of bacteriophages but plasmid profiles were identical (Central Public Health Laboratory 11 July 1986). A fourth isolate was shown to be different only in the plasmid profile.

Four sternal wounds showed pure growth of *Staphylococcus haemolyticus* or *Staphylococcus simulans* and another 23 had a mixture of organisms cultured, mostly Gram-negative species plus coagulase-negative staphylococci (*Table 3*). *Acinetobacter* spp. were the commonest (nine wounds), with smaller numbers of *Enterobacter* spp. (six wounds), *Klebsiella* spp. (four wounds), *Proteus mirabilis* (three wounds) and *Escherichia coli* (three wounds). These were comparable to wounds from which only coagulase-negative staphylococci were isolated but the signs of infection were less marked (Mann–Whitney: total wound score, $P=0·08$; score for clinical appearance, $P=0·02$; score for changes in management, $P=0·7$).

Discussion

S. epidermidis is present on the skin overlying the sternum in 80–90 per cent of the population[8]. It can be isolated easily from theatre air by sampling or on exposed plates, and the counts obtained are in proportion to the number of staff in the theatre and the degree of activity during operation[9,10]. The organisms have a high chance of reaching the operative field and, in the case of cardiopulmonary bypass, can be cultured in over 10 per cent of cases from the blood in the cardiopulmonary

Table 4 *Clinical sequelae of sternal wound infection according to bacterial species isolated*

		Number (and percentage) of patients		
Organism	Total	In-patient stay over 14 days	Antibiotic therapy	Drainage or débridement
Staphylococcus epidermidis	49	13 (27)	5 (10)	7 (14)
Staphylococcus aureus	13	3 (23)	3 (23)	6 (46)

Statistical analysis: in-patient stay and antibiotic therapy. Fisher's test, $P>0·9$; drainage or débridement. $\chi^2=4·5$, difference in proportions $= -0·32$, 95% confidence interval $-0·66$ to $0·02$, $P<0·05$

bypass equipment[11,12]. Other than bypass contamination, these factors are applicable in the generality of surgery and *S. epidermidis* is the organism most commonly causing perioperative contamination in 'clean' surgery.

The vulnerability of the patient is the other factor in the 'seed and soil' concept of wound infection. The immune system is depressed after cardiac surgery[13], and the exposure of the sternum and its subsequent fixation with non-absorbable suture material may contribute to the 1·7 per cent (9/517) incidence of severe sternal infection reported here. Although it seems likely that seeding of *S. epidermidis* into such a wound results in infection, the lack of reliable clinical criteria and the misleading nature of surface cultures has previously made this difficult to prove conclusively[3,14]. In one study of deep sternal sepsis, superficial swabs failed to demonstrate the same organism on culture as mediastinal samples in 7/15 patients[1]. Nevertheless, *S. epidermidis* has been regarded as a presumptive pathogen in previous studies[15,16].

The ASEPSIS wound score ensures that all abnormalities of wound healing are recorded and provides a weighted index proportional to the severity of infection. For severe infections, it correlates well with previously reported studies[2] but has the added strength that it awards a score to all lesser degrees of impaired healing. By including the full spectrum of wound problems related to infection, the statistical power may be increased. The numbers of infections are small, even in this study of 517 patients, and would have been impossible to analyse if only clinically serious infections were available for analysis.

The 49 wounds where *S. epidermidis* was the only isolate were indistinguishable, on any of the criteria used, from the 13 in which *S. aureus* was the presumptive pathogen. The only difference in the clinical sequelae was the greater probability that the wound would be drained or débrided if *S. aureus* was isolated, which may reflect the surgeon's response to isolation of a well-known pathogen. The likelihood that *S. epidermidis* is itself a primary pathogen in wound infection is supported by the finding that, in 16 of the 22 cases where repeated samples were available, the strains found in the second sample matched that in the first. Furthermore, one strain was responsible for severe infection in three different patients.

A rational choice of antibiotic therapy for a wound infection attributable to *S. epidermidis* can be made only if the pathogenic potential of these organisms is recognized in the laboratory and a full range of antibiotic sensitivity tests performed. Wound infection with *S. epidermidis* is clinically just as severe as that with *S. aureus*, and much more common.

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Surgical gloves as a mechanical barrier against human immunodeficiency viruses

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A wide variety of surgical gloves are presently available. Seven different types of gloves were investigated for the ability to prevent transmission of the human immunodeficiency virus (HIV), the causative agent of AIDS. Six types of gloves withstood severe compression tests and also exhibited direct antiviral properties. No penetration of HIV through the intact glove was detected.

Keywords: HIV transmission, surgical gloves, examination gloves

The growing numbers of persons infected with the AIDS or human immunodeficiency virus (HIV) serve to increase the chances of doctor/infected patient contact. Since HIVs have been isolated from blood as well as various body fluids including saliva, cervical secretions, urine and tears[1], all persons who come into contact with blood and body fluids from infected persons (e.g. dentists and nurses) are generally advised to wear surgical gloves. Here we report on the ability of several different types of surgical or examination gloves to function as a mechanical barrier against the HIV family of retroviruses.

Materials and methods

Seven different types of gloves were tested:

type 1, Prototype surgical procedure glove
type 2, Featherlite (surgical procedure glove)
type 3, starch-free Biogel II E.B 12
type 4, starch-free Biogel S 961.1
type 5, Regent Sensor
type 6, Regent Dispo and
type 7, Mediglove medium (often used for vaginal and rectal examinations).

All these gloves were latex except for type 7 which was manufactured from a copolymer of ethylene and methylacrylate. All gloves were obtained from London International

Method

The protective function was examined using two distinct isolates of HIV, the HTLV-IIIB (from Dr R. C. Gallo, NIH) and Ma isolates[2] which have been shown by molecular analysis to have considerable differences in their envelope structures. Ten millilitres of HIV-infected cell suspension containing at least 10 000 infectious units/ml were placed in a glove and the open end tied with a knot. The glove was then placed in a 60 ml syringe (Sabre International Products Ltd) and the plunger depressed 20 times to a maximum pressure exerted with one hand. The nozzle of the syringe was submerged in culture medium with 8166 or JM, CD4-positive leukaemic T cell lines known to be very sensitive to the cytopathic effects (CPE) of HIV, which includes the formation of syncytia or giant fusion cells which are easily detected by light microscopy. The medium and cells were thus sucked into the syringe during each aspiration and returned to the petri dish with each depression of the plunger.

The cultures were monitored daily for the presence of CPE, reverse transcriptase (RT) levels[3] and antigen expression as determined by immunofluorescence (IF)[4]. Aliquots of the above cultures were added to fresh 8166 and JM cells

In order to test for 'seepage' after prolonged contact with virus-producing cultures, the gloves were filled with 5 ml of high titre virus (4 ml producing an RT activity of 50–100 000 counts per minute) and rubbed into the glove using rubber policemen. The gloves were then placed in a cell culture of 8166 and JM cells and aliquots taken every 3 days from both inside and outside the gloves and tested for infectivity as previously described. The anti-HIV effect of the gloves as well as the powder additives (glove starch) were investigated by thoroughly washing the gloves before inserting 5 ml of virus culture which was then monitored for infectivity at 10 min, 1 h and 24 h.

Results

All tests were repeated on at least two occasions.

All the gloves withstood the severe compression tests with the exception of type 7 which burst at the seams. On two occasions for type 3, the knot was not tight enough and seepage occurred and although virus escaped into the test culture medium no infectious virus activity could be detected.

Reverse transcriptase assays showed no leakage of viral activity. *Table 1* shows the absence of virus infectivity through the gloves as determined by CPE and detection of viral antigens by IF.

All the gloves (except type 7) displayed anti-HIV effects, as shown by reduction in infectivity over 24 h (*Figure 1*). These figures did not alter when the additives such as glove starch were thoroughly washed out. Furthermore, glove washings containing glove starch had no effect on HIV infectivity.

Discussion

These results show that all the latex gloves withstood considerable mechanical pressure as well as rubbing with rubber policemen without leaking virus activity. However, formulations for latex gloves vary from manufacturer to manufacturer: therefore, the inhibitory effect of the latex gloves

Table 1 *HIV penetration through the gloves under pressure*

	Day 0	Day 4	Day 7	Day 11	Day 14	Day 18	Day 21
Syncytial formation							
Virus	0	++++	++++	++++	(Most cells dead)		
Medium	0	0	0	0	0	0	0
Types 1–7	0	0	0	0	0	0	0
8166 cells stained with AIDS serum (%) (immunofluorescence)							
Virus	0	25	57	96	—	—	—
Medium	0	0	0	0	0	0	0
Types 1–7	0	0	0	0	0	0	0

++++ = 80 per cent of cells fused in syncytia

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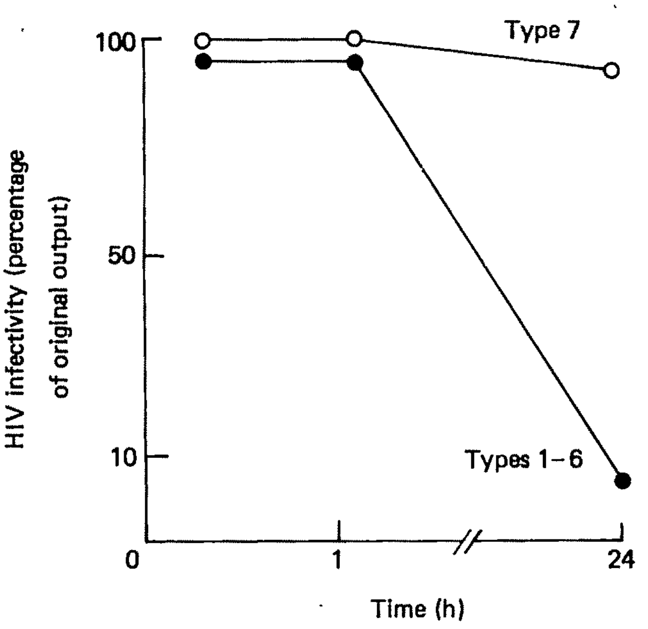

Figure 1 *The infectivity of virus-containing media incubated in gloves for 10 min, 1 h or 1 day was assessed by measuring the cytopathic effect of serial dilutions of media on 8166 cells. The measurements were compared with the virus infectivity of the same virus preparation incubated under the same conditions in 96-well flat-bottomed tissue culture microplates (Falcon). The results are expressed as the percentage of the infectivity of the virus incubated in the microplates*

tested may not automatically be related to gloves from other manufacturers without testing, as has recently been shown for different condoms which do not all protect against HIV penetration satisfactorily[5]. Furthermore, we have shown that contact with types 1–6 gloves (but not type 7) inhibits the subsequent infectivity of HIV. The glove starch additives had no inhibitory properties.

All the studies were performed with very high concentrations of HIV and it is therefore possible that the amount of virus presented by an HIV-infected patient could be inhibited by contact with latex gloves alone. The destruction of virus infectivity by the seepage through a knot tied in type 3 gloves is most remarkable. It therefore seems likely that, with the exception of a needle puncture or knife excision through the glove and skin, the latex gloves tested provide adequate protection for the medical operative when dealing with HIV-infected persons. The recent reports of HIV transmission to three persons who were exposed to HIV-positive blood without any barrier protection[6] serves to underline the need for effective health care worker protection. However, over 200 reported needle stick injuries in medical attendants have not resulted in seroconversion to HIV and in the one known case in the UK, a considerable volume of infected blood was accidentally injected into a finger[7]. Thus, it would appear possible that latex gloves may offer some protection to minor cuts and abrasions with HIV-infected material.

Acknowledgement

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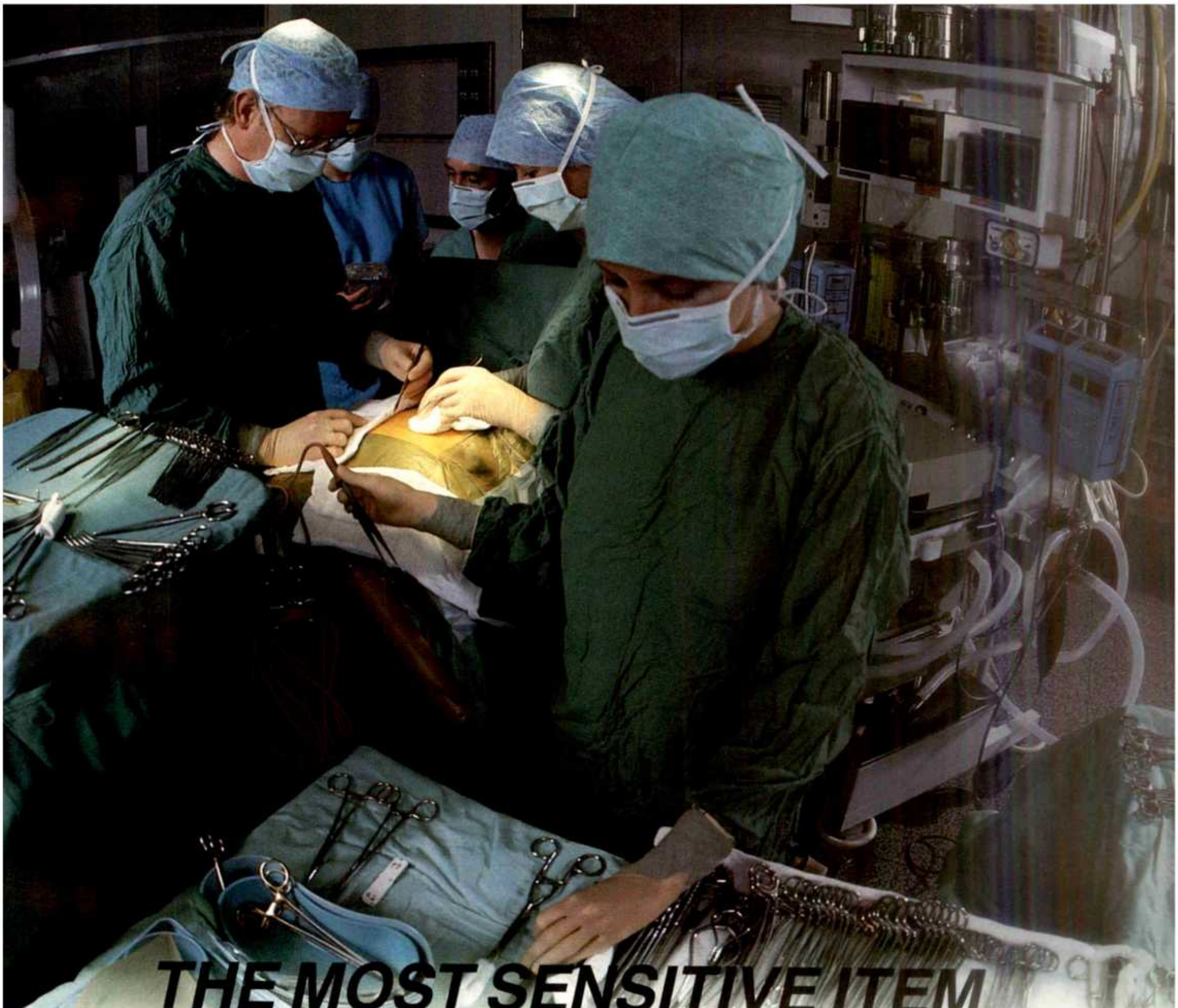

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Aggressive treatment of severe diffuse peritonitis: a prospective study

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In a prospective study of 22 patients with diffuse peritonitis managed by the method of electively staged multiple laparotomies, the abdomen was left open in 9 patients. The patients were selected on the basis of the severity of their intra-abdominal infection: only massive faecal peritonitis, postoperative peritonitis and pancreatic abscesses were included. These amounted to only 9 per cent of all patients with intra-abdominal infection treated over a 2-year period. Up to seven re-operations were required per patient. In view of a high mortality rate of 32 per cent, the superiority of this aggressive management strategy over conventional methods is not fully established.

Keywords: Peritonitis, open management, planned relaparotomy

The traditional surgical treatment of severe, diffuse peritonitis has proved disappointing, as evidenced by prohibitive mortality figures[1]. This has stimulated the search, in recent years, for more aggressive forms of management. Initially promising methods, such as radical peritoneal débridement[2] or continuous postoperative peritoneal lavage[3], failed to gain wide acceptance. Poor results have been obtained with repeated laparotomies 'on demand', subordinate to the appearance of clinical signs of residual sepsis or the development of remote organ failure[4,5]. Furthermore, to the best of our knowledge no controlled study has ever shown that local, intraperitoneal instillation of various antiseptics or antibiotics has resulted in a decreased mortality rate in patients who already receive wide-spectrum peri-operative systemic antibiotics[6].

'Electively staged (or planned) laparotomies' and 'open management of the abdomen' are modern concepts which have come recently under intense scrutiny as evidenced by a growing number of reports[5,7–11] and review articles[12,13]. In these series, the criteria for patient selection are not always stringent enough, as varying degrees of sepsis severity are studied: this, of course, may generate inappropriate enthusiasm for these demanding management modalities when, at least in some cases, similar good results could have been achieved by simpler methods.

In this limited prospective study of patients selected on the basis of the severity of their initial peritonitis, we have attempted to evaluate the method of selectively planned relaparotomies supplemented, when necessary, by open management.

Patients and methods

Patient selection

During the 24-month period (January 1985–December 1986), 246 patients underwent emergency operations for peritonitis. Of these, 22 patients (9 per cent) were selected to undergo the aggressive management policy reported in this study. Sixteen patients were men and six women; their ages ranged from 23 to 78 years.

This method of treatment was consistently applied in all patients suffering from diffuse peritonitis originating from colonic or pancreatic sources or developing following abdominal surgery, in these settings a high mortality rate can be expected[1,14]

Patients with localized intra-abdominal infection or peritonitis originating in the upper gastrointestinal tract, small bowel, biliary system, appendix and urogenital organs are known to have a better prognosis. We treated them conventionally and they are excluded from this study. The characteristics of our patients, with the specific causes of the intra-abdominal infection, are summarized in *Table 1* In brief, 13 patients suffered from diffuse faecal peritonitis, 4 had peripancreatic suppuration or infected pancreatic necrosis and 9 patients developed peritonitis (faecal in some cases) following abdominal surgery; in 7 instances, the primary operation was performed at another hospital The APACHE II score[15] was determined for each patient before our first laparotomy for peritonitis.

Management modalities

All patients were treated in the surgical intensive care unit until no further relaparotomy or organ support was necessary. Wide-spectrum antibiotic therapy, a combination of penicillin, an aminoglycoside and metronidazole, was started pre-operatively and subsequently modified according to culture results. At the first laparotomy for peritonitis, the source of contamination was eradicated in the usual way. When bowel resections were required, ostomies were performed instead of anastomoses. The peritoneal cavity was generously irrigated with a warmed solution of normal saline. The indication for the policy of planned relaparotomies was determined at the time of the first operation, in accordance with our selection criteria The abdomen was then re-explored every 2–3 days, irrespective of the patient's clinical condition. At reoperation, all septic collections were drained; radical débridement, consisting of the removal of the fibrinous 'peel' from the intestines and peritoneal wall, was not carried out. The use of abdominal drains was obviated by the plan for an early re-exploration. The decision to discontinue the abdominal re-explorations was taken on the finding of a macroscopically clean peritoneal cavity On completion of the last laparotomy, drains were placed in those cases where potentially infected collections were thought likely to form. The abdomen was closed 'en masse' whenever possible and the skin left open with a povidone–iodine pack. When the abdomen had to be left open, we used the 'sandwich technique'[16] consisting of a Marlex mesh (C R. Bard Inc., Massachusetts, USA) applied over the bowel and omentum and sutured to the edges of the fascia, an OpSite adhesive drape (Smith and Nephew Ltd, UK) covering the defect, and suction–irrigation tubes interposed between these two layers. At every operation the adhesive drape is discarded and the abdomen is entered by incising the Marlex mesh, this is repaired at the end of the operation. On occasion a zipper was sutured in the centre of the mesh When additional operations were deemed no longer necessary, the abdomen was formally closed. If a Marlex mesh was used, it was removed 2 weeks after the last laparotomy and a split-thickness skin graft immediately applied over the thin granulation tissue overlying the mesh *in situ*: in our earlier experience, mesh extrusion through the graft occurred, necessitating piecemeal excision of the loose foreign material.

Results

Fifty-five relaparotomies were performed: the required number of reoperations ranged from none, in a patient who died before re-exploration could be undertaken, to seven; there were on average 2·5 reoperations per patient. In 7 out of the 21 patients (33 per cent) who underwent the first relaparotomy no faecal material or pus was discovered at operation: no more re-explorations were performed in these patients. Seven patients died (32 per cent): five deaths were accounted for by multiple organ failure, one critically ill patient (APACHE II score of 22)

Table 1 *Patients' characteristics*

Patient No.	Age	Sex	Diagnosis	APACHE II score	No of reoperations	Abdominal closure	Outcome
1	74	M	Strangulated diaphragmatic hernia. Faecal peritonitis	16	1	Yes	A
2	69	M	Perforated gastrocolic fistula. Faecal peritonitis	15	2	Yes	A
3	23	M	Postoperative leak of colonic repair. Faecal peritonitis	10	4	Yes	A
4	36	M	Pancreatic abscess and colonic necrosis	11	2	MM	A
5	34	M	Rectal perforation. Faecal peritonitis	10	3	Yes	A
6	29	M	Dehiscence of Hartmann's pouch. Faecal peritonitis	8	2	Yes	A
7	42	M	Pancreatic abscess and colonic necrosis	21	2	MM	D
8	27	M	Caecal necrosis after appendicectomy. Faecal peritonitis	5	1	Yes	A
9	47	F	Perforated sigmoid diverticulum. Faecal peritonitis	5	1	Yes	A
10	44	M	Colonic injury and postoperative infected mesenteric haematomata	20	3	MM	D
11	73	F	Perforated colonic carcinoma. Faecal peritonitis	11	1	Yes	A
12	50	F	Postoperative ischaemic colonic necrosis. Faecal peritonitis	12	2	MM	A
13	50	M	Pancreatic abscess	18	3	MM	D
14	40	M	Left colonic injury, diffuse retroperitoneal sepsis. Faecal peritonitis	16	3	Yes	A
15	55	M	Leaking duodenal stump after gastrectomy	6	3	Yes	D
16	63	F	Perforated gastrojejunocolic fistula. Faecal peritonitis	22	0	Yes	D
17	78	M	Postoperative dehiscence of enterotomy	22	1	MM	A
18	52	F	Postoperative biliary peritonitis after common bile duct exploration	23	5	MM	D
19	63	M	Dehiscence of pyloroplasty and fasciitis of the abdominal wall	13	1	MM	D
20	38	F	Pancreatic abscess	8	5	MM	A
21	36	M	Perforated amoebic colitis Faecal peritonitis	10	7	Yes	A
22	77	M	Perforated colonic carcinoma. Faecal peritonitis	11	1	Yes	A

Outcome: A, alive; D, dead; MM: abdomen left open with a Marlex mesh

died immediately after the first operation and another one succumbed to a pulmonary embolus 4 weeks following his last operation. Twelve out of the thirteen patients with faecal peritonitis survived.

The abdomen was closed in 13 patients who required an average of 2·2 relaparotomies. In one patient (Case no. 21), closure could be achieved after each of the seven relaparotomies. Two patients (15 per cent) died in this group. The abdomen was left open with a Marlex mesh in nine patients; this was inserted at the primary operation in six instances, at the first re-exploration in two patients and at the second re-exploration in one. The average number of relaparotomies was 2·9 in this group; five patients (56 per cent) died.

In seven (47 per cent) of the survivors, small amounts of infected fluid drained spontaneously via drains placed at the time of the last laparotomy. No reoperation was required for persistent or recurrent intra-abdominal sepsis.

In all the survivors who underwent abdominal closure, skin healing occurred by secondary intention. Four of the patients treated by the open method survived: three of them underwent early excision of the mesh and immediate split-thickness skin grafting with excellent results; one patient had a subsequent repair of his incisional hernia and the other two were satisfied with a binder. In the fourth patient (Case no. 12) a respiratory infection delayed the excision of the Marlex mesh, resulting in a small-bowel fistula for which three subsequent operations were required. Thirteen of the survivors returned to a normal life. The APACHE II score ranged from 5 to 23 with a mean of 13·2; the mean score was 11·3 in the survivors and 17·5 in the patients who died.

Discussion

Diffuse peritonitis is not a homogeneous disease; its outcome depends largely on its site of origin[1]. The evaluation of aggressive treatment modalities such as planned relaparotomies and open management of the abdomen poses the problem of patient selection. We elected to submit to this management protocol only a small proportion (9 per cent) of our patients with peritonitis. Our cases were selected on the basis of the severity of the infection: diffuse faecal peritonitis and postoperative peritonitis due to suture-line disruption are known to be associated with the highest mortality[1]; we also included patients with suppurative pancreatitis as, in these, the treatment is notoriously difficult because of the protracted nature of the purulent and necrotizing process. The conventional 'once for all' laparotomy often fails in severe diffuse peritonitis because of the propensity for septic or frankly purulent collections to re-form in spite of adequate eradication of the primary intra-abdominal source of contamination. The use of various forms of intraperitoneal drains offers no more than an illusory sense of security. Electively planned reoperations constitute the cornerstone of our aggressive management. The rationale for this policy is to anticipate the formation of septic collections and to preclude, before they have become clinically apparent, their deleterious systemic effects.

At operation, we have avoided the performance of primary anastomoses: ostomies were fashioned instead. In the series of planned relaparotomies reported by Teichmann *et al.*[7], a high incidence of suture-line disruption occurred: all the duodenal stumps in their series broke down after primary closure, as well as 20 per cent of their intestinal anastomoses.

Any electively staged re-exploration is justified, in retrospect, on the finding of infected collections of tissue in need of further débridement; such a re-look may be termed 'unnecessary' when the displayed peritoneal cavity is found to be relatively clean. This occurred in seven out of our twenty-one patients (33 per cent) submitted to their first relaparotomy, a similar rate (29 per cent) of negative laparotomies was reported by Penninckx *et al.*[5] in their retrospective study. Although a refinement of our selection criteria may decrease the rate of these 'unnecessary' explorations, this is a relatively small price to pay.

Table 2 *Collective series of patients managed by planned relaparotomies with or without open abdomen*

Authors	No. of patients	Indication*	Mortality (%)	Mean score†
Penninckx *et al.*[5]	31	IAI	9 (29)	—
Teichmann *et al*[7]	61	IAI	14 (23)	APACHE II 23
Duff and Moffat[8]	18	IAI	7 (39)	—
Maetani and Tobe[9]	13	IAI	2 (15)	—
Anderson *et al.*[10]	20	IAI	12 (60)	—
Mughal *et al.*[11]	18	IAI and PRS	5 (28)	Sepsis score 18
Wouters *et al.*[20]	20	IAI	4 (20)	—
Steinberg[21]	14	IAI	1 (7)	—
Goris[22]	26	IAI	13 (50)	—
Pichlmayer *et al.*[23]	37	IAI	15 (41)	—
Stone *et al.*[24]	36	PRS	7 (19)	—
Bradley and Fullenwider[25]	20	PRS	3 (15)	—
Hay *et al*[26]	64	IAI and PRS	34 (53)	—
Champault *et al.*[27]	27	IAI and PRS	13 (48)	—
Charleux *et al*[28]	9	IAI	6 (67)	—
Voyles *et al.*[29]	29	IAI and AF	7 (24)	—
Nel[30]	20	IAI	5 (25)	—
Hedderich *et al*[31]	10	IAI and PRS	2 (20)	APS 16
Chan and Esufali[32]	21	IAI and PRS	6 (29)	—
Pemberton *et al*[33]	17	PRS	3 (18)	—
Wertheimer and Norris[34]	10	PRS	2 (20)	—
Broome *et al*[35]	30	IAI	14 (47)	—
Total	551		184 (33)	

* IAI, intra-abdominal infection; PRS, pancreas-related sepsis, AF, abdominal fasciitis

† APACHE II, acute physiological and chronic health evaluation; APS, acute physiological score

Support for the early eradication of infected collections is provided by the uncertainty that established multiple organ failure secondary to sepsis may be reversed by the mere control of the septic focus[17].

The immediate purpose of a re-exploration is to evacuate potentially or frankly septic collections which have formed over the preceding 48–72 h. The decision to discontinue the re-explorations was taken when the peritoneal cavity was macroscopically clean (that is free of frankly purulent collections or necrotic tissue) or when only a small localized collection of infected exudate was found; in this case, an intraperitoneal drain was placed *in situ*. In seven (47 per cent) of the survivors, small amounts of infected fluid drained to the exterior over a few days; none of these patients needed percutaneous or operative drainage of a persistent collection; this contrasts with the occurrence of late intra-abdominal abscesses in six out of forty-seven survivors in a study[7] where no drains were inserted at the time of the last laparotomy.

The open management of the septic abdomen has emerged as a corollary to the policy of repeated laparotomies: if the abdomen is to be re-explored every 48 h, why close it at all? The emphasis on maximal drainage of the whole abdomen is underlined by the now fashionable term of 'laparostomy' which has permeated from the French[18] into the English language literature[11]. However, contrary to early claims, leaving the septic abdomen open does not obviate the need for thorough re-explorations, searching for deep pockets of pus[9]. The advantages of the technique have become apparent: necrosis of the abdominal wall closed forcefully and repeatedly in the presence of an ileus and oedema of the parietes is avoided; a better diaphragmatic excursion may be expected; a lower intra-abdominal pressure exerted on the kidneys results in their improved perfusion[19], and exposure of the peritoneal cavity to air may perhaps minimize the role of anaerobic organisms. Complications do occur: spontaneous fistulae in exposed intestinal loops; risks of evisceration; massive fluid losses; and potential contamination of the open wound. The use of Marlex (polypropylene) mesh has emerged as a promising solution to these difficulties[16,20]. Eventual closure of the abdominal defect must be addressed once the sepsis has subsided. Because of the problems associated with the practical implementation of this technique and the need for subsequent reconstruction of the abdominal wall, the decision to leave the abdomen open is not taken lightly: the build of the patient, the volume of the septic exudate, the degree of intestinal ileus, the amount of parietal inflammation, and the expected number of necessary abdominal re-explorations are pertinent considerations. We have treated our patients by the closed method whenever possible; the open management had however to be used in nine out of twenty-two patients (41 per cent), reflecting the frequent impossibility of closing the abdomen satisfactorily in patients submitted to multiple laparotomies over a short period.

The abdominal wound is treated when recovery is well under way, and the mesh is removed on the fourteenth day after the last laparotomy, with immediate split-skin grafting of the underlying granulation tissue covering omentum and intestinal loops. The resulting wide-necked ventral hernia can be repaired at a later stage. Out of our four survivors treated by the open method, only one underwent repair of his incisional hernia, the other three are not incapacitated by their hernia or by a less than optimal cosmetic result.

In a review of the recent literature, we have collected 551 patients treated aggressively for intra-abdominal sepsis (*Table 2*). The abdomen was managed by the open technique in all these series except one[5]. Our mortality rate of 32 per cent is very similar to the calculated mortality rate of 33·3 per cent in the collective series.

Multiple organ failure was responsible for the death of five out of seven patients in our study. It seems that even the most aggressive treatment of the primary septic focus is not sufficient to reverse established multiple organ failure[17] which is thought to be perpetuated by severe generalized inflammation caused possibly by activated complement and tissue anoxia[36]. In this study, as in the collected cases, one-third of the patients succumb to severe intra-abdominal infection despite the aggressive surgical management. The value of this surgical strategy rests on the clinical observation that the conventional treatment of severe intra-abdominal infection is bound to fail, in at least a proportion of patients, mainly because residual or recurrent sepsis perpetuates or aggravates multiple organ failure. Even if these novel techniques have indeed improved, even marginally, the outcome of patients with intra-abdominal infection, progress in the operative treatment of severe peritonitis may have reached its limits.

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Effect of splenectomy on Gram-negative bacterial clearance in the presence and absence of sepsis

Severe sepsis leads to depression of the reticulo-endothelial system (RES) with delayed bloodstream clearance of particulate matter and bacteria. Splenectomy results in increased susceptibility to infection with encapsulated organisms but its effect on the resistance to postoperative Gram-negative infection has been little studied. We have investigated the effect of splenectomy on RES function by measurement of plasma fibronectin concentrations and bacterial clearance in the presence and absence of sepsis. In experiment 1, rabbits underwent splenectomy (n = *8*) *or laparotomy only* (n = *8*) *4 weeks before a second laparotomy. In experiment 2, animals had either splenectomy* (n = *8*) *or laparotomy only* (n = *8*) *followed 4 weeks later by devascularization of the appendix (sepsis). Plasma fibronectin concentrations and the blood clearance and organ distribution of an intravenous injection of* ^{75}*Se-labelled viable* Escherichia coli *(2–3 ×* 10^8 *colony forming units (c.f.u.)) were measured 24 h after the second operation. Splenectomy resulted in: (1) a persistent reduction in plasma fibronectin concentration in the presence and absence of sepsis, and (2) a delay in the bloodstream clearance with reduced hepatic (Kupffer cell) uptake of* E. coli *which was exaggerated in the septic splenectomized animal. It is concluded that the spleen may be important for Gram-negative bacterial clearance, possibly related to its influence on plasma fibronectin concentration and Kupffer cell function.*

Keywords: Postsplenectomy sepsis, Gram-negative sepsis, reticulo-endothelial function, plasma fibronectin

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Postsplenectomy sepsis has become a well-recognized condition in children since the first clinical report by King and Schumacker in 1952[1] but recent evidence suggests that adults after splenectomy also have an increased susceptibility to infection[2,3]. The pneumococcus is the major causative organism of postsplenectomy sepsis (50 per cent of cases)[4] and the importance of the spleen for its clearance and that of other encapsulated organisms is accepted. Eleven per cent of cases of postsplenectomy sepsis are due to *Escherichia coli* but neither the influence of the spleen on Gram-negative infection nor the effect of splenectomy on patients who are at risk from postoperative Gram-negative infection has been established.

One component of host defence, the reticulo-endothelial system (RES), is important for the clearance of particulate matter and bacteria from the bloodstream. Failure of the RES, as occurs in sepsis, may be due to deficiency of opsonins and/or intrinsic macrophage dysfunction. Both may be important in the pathophysiology of postsplenectomy sepsis. Reticulo-endothelial function may be measured directly by colloid clearance techniques or indirectly by the measurement of plasma fibronectin concentrations. The clearance kinetics of ^{75}Se-labelled *E. coli* are similar to those of low-dose technetium tin colloid[5]. There is experimental evidence that the former can be used as an RES test agent to measure RES function during sepsis[6].

Plasma fibronectin may be an opsonin of the RES important for the clearance of particulate matter and changes in its concentration have been shown to correlate with RES function measured by colloid clearance techniques[7].

The aims of this study were to investigate in the rabbit the effect of splenectomy, in the presence and absence of sepsis, on RES function by the measurement of both plasma fibronectin concentrations and Gram-negative bacterial clearance.

Material and methods

Animals

Male New Zealand white rabbits (2·5–3·0 kg) were used. The animals were caged separately and allowed free access to food and water.

Surgical procedures

Two operations were performed 1 month apart through midline incisions under general anaesthesia with sodium pentobarbitone (Sagatal, May and Baker). At the first operation rabbits underwent either splenectomy or laparotomy. The spleen was removed after ligation and division of its segmental blood supply together with splenunculi present in three of sixteen (19 per cent) animals. The abdomen was closed and the animals returned to their cages for 1 month. At the second operation rabbits underwent either laparotomy only (experiment 1) or laparotomy with induction of sepsis (experiment 2).

Septic model. Peritonitis was induced in the rabbit by devascularization of the appendix. The previous midline incision was opened and the appendix identified. The arcade of vessels between the appendix and small bowel, and the main appendicular artery and vein were ligated and divided. The appendix was left *in situ* and the abdomen closed. RES function was measured 24 h after the second operation.

Preparation of radiolabelled bacteria

Viable *E. coli* from a human blood culture isolate were grown in a methionine-free medium to which 3·7 MBq of [^{75}Se] selenomethionine (Amersham International PLC) had been added. Selenomethionine acts as a pseudo-amino acid and in the absence of methionine becomes incorporated into the bacterial cell wall. After 48 h incubation at 37°C when optimum growth had occurred, the bacteria were centrifuged and washed twice with saline to remove excess [^{75}Se] selenomethionine which had not been incorporated into cell wall proteins. The final pellet of *E. coli* was suspended in 4 ml of saline which was sufficient to study

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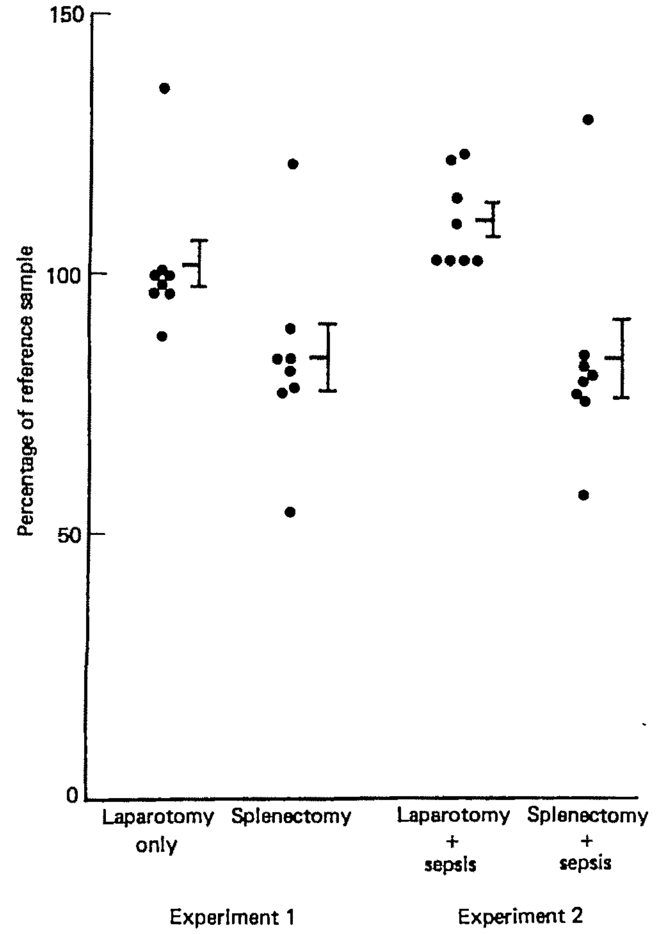

Figure 1 *Plasma fibronectin concentrations. Experiment 1. laparotomy only* versus *splenectomy*, P<0·05; *experiment 2: laparotomy and sepsis* versus *splenectomy and sepsis*, P<0·05

two animals. The concentration of viable bacteria in the radiolabelled sample was determined by counting the number of colony forming units (c.f.u.) in a diluted aliquot plated on to nutrient agar for 24 h.

Measurement of RES function

Animals were lightly anaesthetized with intravenous sodium pentobarbitone and blood taken for plasma fibronectin estimation and culture before being administered a 1 ml bolus of radiolabelled *E. coli* (1–3 × 10^8 c.f.u.) rapidly via an ear vein. Serial blood samples were taken over 45 min from a vein in the contralateral ear. The animal was killed with an overdose of anaesthetic, a peritoneal culture was taken and the liver and lungs removed. The activity of the blood and organs was measured using a LKB-Wallac 80 000 gamma counter. Blood clearance curves were constructed and analysed using a Hewlett Packard desk-top computer (HP9845B) running a pharmacokinetic program modified to correct for radioactive decay and incorporating statistical analyses. The half-life of the clearance of *E. coli* from the bloodstream was calculated from the first and fastest component of clearance[8]. Uptake of radiolabelled bacteria by the organs was measured by counting aliquots of homogenized liver and lung in the gamma counter using 1 ml of radiolabelled *E. coli* as a standard. The results are expressed as a percentage of the injected dose per gram of tissue.

Plasma fibronectin assay

Blood for plasma fibronectin estimation was collected in paediatric EDTA polystyrene tubes, centrifuged immediately and the plasma removed for storage at −70°C. Plasma fibronectin concentrations were assayed by an immunoturbidimetric method using commercially available antiserum[9]. The results are expressed as a percentage of the mean value of pooled plasma from six unanaesthetized rabbits kept under the same conditions as the test animals.

Statistical analysis was by the two-tailed Mann–Whitney *U* test.

Results

Experiment 1

Post-mortem examination was normal apart from a few intraperitoneal fibrinous adhesions.

Bacteriology. All blood and peritoneal cultures were negative.

Plasma fibronectin. The plasma fibronectin results are shown in *Figure 1*. There was a significant reduction in the concentration of fibronectin in the plasma after splenectomy.

Clearance kinetics. The clearance of *E. coli* from the bloodstream ($t_{\frac{1}{2}}$) is shown in *Figure 2*. There was a delay in bacterial clearance after splenectomy, as shown by the statistically significant increase in $t_{\frac{1}{2}}$.

Organ distribution of E. coli. The distribution of *E. coli* to the liver and lungs is shown in *Figure 3*. In splenectomized animals the uptake of radiolabelled *E. coli* by the liver was significantly reduced but there was no difference in pulmonary uptake.

Experiment 2

The post-mortem findings in all animals were a large gangenous appendix, peritonitis and fibrinous adhesions.

Bacteriology. The results of blood cultures taken before the injection of viable bacteria and peritoneal cultures taken at the time of animal death (24 h) are shown in *Table 1*. Half of the blood cultures and seven of eight of the peritoneal cultures were

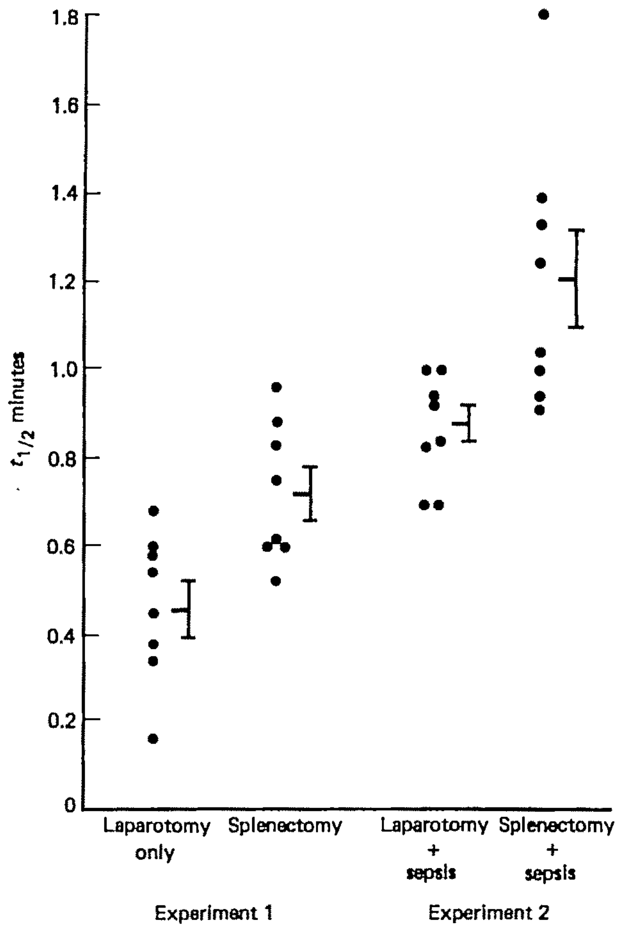

Figure 2 *Rate of blood clearance of* ^{75}*Se-labelled* E. coli. *Experiment 1: laparotomy only* versus *splenectomy*, P<0·05; *experiment 2: laparotomy and sepsis* versus *splenectomy and sepsis*, P<0·05

positive, confirming that all animals had severe sepsis when RES function was studied.

Plasma fibronectin. The plasma fibronectin results are shown in *Figure 1*. Plasma fibronectin concentrations were raised in those animals which underwent laparotomy with the induction of sepsis. However, plasma fibronectin concentrations were significantly reduced if splenectomy had preceded the induction of sepsis. The concentrations were similar to those produced by splenectomy alone in experiment 1.

Clearance kinetics. The results of the blood clearance of radiolabelled *E. coli* in both sepsis groups are shown in *Figure 2*. There was a statistically significant delay in bacterial clearance in both groups, as shown by the increased half-lives. On comparing those animals which had laparotomy and induction of sepsis with the laparotomy only group in experiment 1, the delay in bacterial clearance reached significance at the 0·1 per cent level. The delay in the clearance of *E. coli* was even greater in those animals which underwent splenectomy in addition to the induction of sepsis.

Organ distribution of E. coli. The distribution of *E. coli* to the liver and lungs is shown in *Figure 3*. There was a significant reduction in the uptake of radiolabelled *E. coli* by the liver in both sepsis groups when compared with the laparotomy only group in experiment 1. The reduction was significantly greater for those animals which underwent splenectomy and the induction of sepsis.

There was an increase in the pulmonary localization of bacteria in the laparotomy and sepsis group but this did not reach statistical significance at the 5 per cent level.

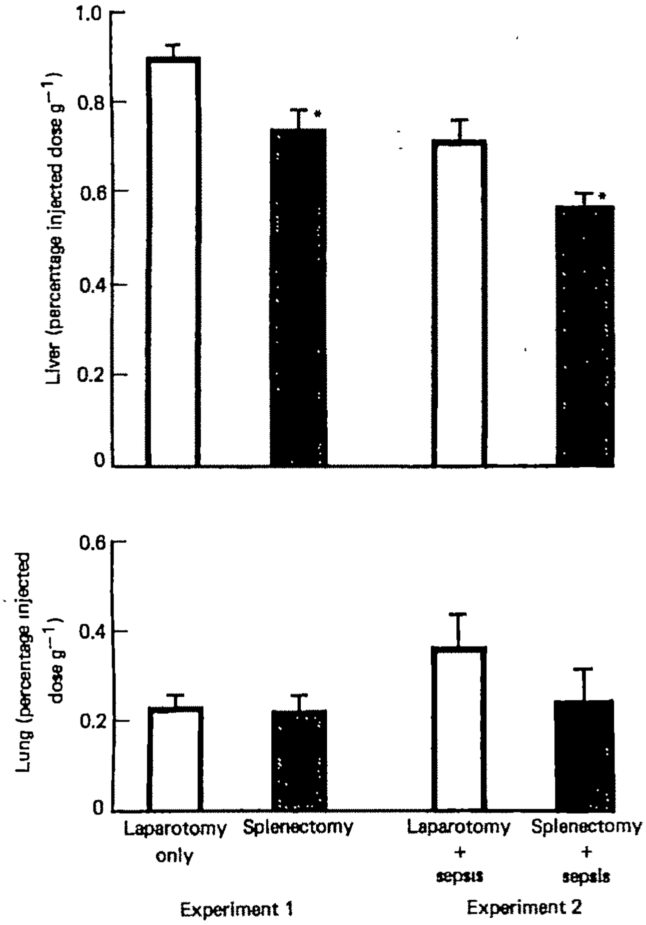

Figure 3 *Organ distribution of* ^{75}*Se-labelled* E. coli * $P<0·05$

Discussion

There have been several large reviews reporting overwhelming postsplenectomy infection in children[4,10,11] but it is now apparent that splenectomy in adults carries a small but definite risk of bacterial sepsis which is associated with a late morbidity and mortality[2,3].

The pathophysiology of postsplenectomy sepsis is unknown but may be due to altered RES function and in this respect the interrelated cellular (phagocytosis) and humoral (production of antibodies) functions of the spleen need to be examined. Acting as a reticulo-endothelial organ, the spleen has a greater capacity than the liver per unit weight for the uptake of organisms. Experimental studies have shown that splenectomized animals injected with pneumococci have higher blood concentrations of bacteria several hours after injection, and an increased mortality[12,13]. This increased susceptibility to infection is thought to be due to the absence of splenic clearance. However, splenectomy has been shown to increase susceptibility to infection with *E. coli*[14], an unencapsulated bacteria normally cleared predominantly by the liver[15], and to worsen the prognosis for peritonitis induced by caecal ligation which is also associated with organisms (enterobacteria) normally cleared by the liver[16]. In our study, in which viable *E. coli* were given by intravenous injection into rabbits 1 month after splenectomy, there was a delay in the bloodstream clearance of the bacteria associated with a significant reduction in their hepatic (Kupffer cell) localization. These changes were even greater in those animals which had intra-abdominal sepsis in addition to splenectomy. Another study has shown a temporary reduction in the hepatic uptake of the RES test agent, lipid emulsion, 4–8 h after splenectomy but this returned to normal within 2 days[16]. Grover *et al.* showed no difference in the hepatic localization of pneumococci but the proportion of viable bacteria remaining in the liver after several hours was much greater in splenectomized animals[17]. They concluded that splenectomy resulted in impairment or saturation of hepatic bactericidal function. Therefore, absence of splenic phagocytic function may contribute to the reduced efficiency of bacterial clearance but the significant reduction in the localization of *E. coli* by the liver, in our study, seems to be of greater importance and implies that the spleen influences Kupffer cell function, possibly through a humoral mechanism or by a reduction in opsonization.

Table 1 *Bacteriology of blood and peritoneal cultures from experiment 2*

	Positive cultures	
Group	Blood	Peritoneal
Laparotomy + sepsis, $n=8$	4	8
Splenectomy + sepsis, $n=8$	4	7
Organisms cultured	*Clostridium* sp. *Bacteroides fragilis*	*Clostridium* sp. *Escherichia coli* *Streptococcus faecalis* *Bacteroides fragilis* *Bacillus* sp.

Altered concentrations of plasma opsonins have been noted after splenectomy, including reduced serum concentrations of IgM and complement (C3, C5), which are important for the phagocytosis of encapsulated organisms, including pneumococci and *Haemophilus influenzae*[18,19]. Others have reported normal concentrations of IgM and complement[3,20]. Plasma fibronectin, an adhesive glycoprotein, may be an opsonin of the RES important for the clearance of non-bacterial particulate matter and some bacteria. It has specific binding sites for staphylococcal and streptococcal lipoteichoic acid. Its site of synthesis is not known but is thought to be predominantly the liver, as an isolated rat liver preparation has been shown to produce fibronectin at a rate comparable to fibronectin input in a study of fibronectin kinetics[21,22]. The reduction in plasma fibronectin found after splenectomy in this study indicates that the spleen may influence its production. One other study has shown a reduction of plasma fibronectin concentrations in rats at a similar interval after splenectomy[23] but in another study where concentrations were measured for only 10 days after splenectomy there was no reduction[24].

Acute depletion of plasma fibronectin occurs after trauma and operations followed by a rapid return to normal or supranormal concentrations[25]. Plasma fibronectin remains depressed in man during sepsis and endotoxaemia but animal models of acute sepsis, including the laparotomy and sepsis group in this study, show the two-phase response and develop supranormal concentrations after an initial depression[25,26]. After splenectomy, plasma fibronectin concentrations remained depressed in those animals in which sepsis was induced, which supports our suggestion that the spleen influences plasma fibronectin production. It may be hypothesized that the spleen is an important site for fibronectin synthesis but a more plausible explanation may be that the spleen influences the hepatic production of plasma fibronectin, possibly through a humoral mechanism.

This study demonstrates that the spleen is important for Gram-negative bacterial clearance and influences both plasma fibronectin concentration and Kupffer cell function in our animal model. Although experimental work cannot be directly applied to clinical practice, this study suggests that splenectomy may be an additional risk for the surgical patient exposed to Gram-negative infection and therefore provides further support for the concept of splenic preservation.

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Approach to ingrowing toenails: the wedge resection/segmental phenolization combination treatment

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One hundred and seventy procedures were performed on one hundred and forty patients with ingrowing toenails. Each patient was randomly allocated to one of three treatment groups. There were 55 wedge resections (WR), 53 segmental phenolizations (SP) and 62 wedge resection/segmental phenolization combination treatments (WR/SP). All patients were followed up for 6 months. The duration and intensity of postoperative pain was assessed and the recurrence rate monitored. Postoperative pain was less in the WR/SP group ($9{\cdot}4 \pm 13{\cdot}5$ h) than in the WR group ($30{\cdot}0 \pm 37{\cdot}6$ h, $P<0{\cdot}001$). There were seven recurrences in the WR group, four in the SP group, and none in the WR/SP group. The results in the WR/SP group were statistically significant when compared with the WR group ($P<0{\cdot}01$) and with the SP group ($P<0{\cdot}05$). We conclude that the WR/SP combination procedure is a superior form of treatment for ingrowing toenails.

Keywords: Ingrowing toenails, general surgery (foot)

Ingrowing toenail is a common and painful condition affecting adolescents, predominantly, and causing much disability. Patients are often treated by chiropodists, general practitioners and casualty surgeons, before being referred for definitive treatment. There are many options in the treatment of this condition ranging from simple conservative approaches to relatively extensive surgical procedures, requiring considerable operative experience.

In general, procedures of nail bed (germinal matrix) ablation by surgical excision, i.e. wedge resection (WR), as described by Watson-Cheyne[1] or by chemical agents, i.e. segmental phenolization (SP), offer the lowest recurrence rates, ranging from 1·7 to 7·4 per cent[2–4]. Nevertheless, recurrences do occur.

Incomplete nail bed ablation after WR is due to an inadequate surgical technique. Recurrences following SP are due to inadequate phenol penetration of bulky nail beds.

A combination of surgical and chemical ablation of the nail bed for the treatment of ingrown toenails has not been tried. Theoretically, this approach seems a reasonable progression in the aim for complete nail bed ablation. By debulking the nail bed first with the standard WR any small amount of nail bed left *in situ* may subsequently be destroyed chemically by phenolization to achieve complete ablation. Thus, we decided to look at recurrence rates in a new technique using combined WR and SP by carrying out a randomized controlled study, comparing this new combination treatment with the two established treatments of WR alone and SP alone.

Patients and methods

Patients were referred to our ingrown toenail clinic from general practitioners and from the accident and emergency department. All procedures were carried out by a single junior trainee surgeon (M.I.). When suppuration was present, it was treated initially by Eusol soaks and Vaseline gauze dressings on a daily basis, until dry. Oral antibiotics were only prescribed when cellulitis was present. Surgical treatment was instituted as soon as the nail and skin fold were dry. Each toe was randomly allocated, using random numbers, to one treatment group. The toe was cleaned with povidone-iodine solution. A tourniquet was applied and a ring block was given using equal volumes of 0·5 per cent bupivacaine (Marcaine®) and 1 per cent lignocaine (Xylocaine®). Less than 5 ml of local anaesthetic agent readily achieved full toe anaesthesia in most cases.

Wedge resection

The technique used for WR was similar to that described by Winograd in 1929[5]. The nail fold on the affected side was incised exposing the nail bed. The area to be excised included approximately 4 mm of the lateral nail and its bed which was initially marked by incising the edges with a scalpel, then excised down to periosteum using a curette. A single nylon 4–0 suture was applied to the nail fold incision and after a pressure dressing had been applied, the tourniquet was removed.

Segmental phenolization

The technique used for SP was that described by Ross in 1969[6].

Approximately 4 mm of the affected nail edge was removed without incising the nail fold or excising the nail bed. Eighty per cent phenol BP was then applied to the nail bed under the nail fold for 3 min, using an obliquely cut orange stick with a wisp of cotton wool at its end. Care was taken to prevent spillage of phenol onto the skin and the residual phenol was neutralized with methylated spirits.

WR/SP combination treatment

WR was performed exactly as described above, and was followed by the application of phenol for 3 min to the area of the original nail bed in the same manner as described above. A single nylon 4–0 suture was then applied, and the wound was dressed and the tourniquet was removed.

All patients returned to the clinic on the first, fourth and seventh postoperative days. The suture was removed on the seventh postoperative day and the duration and intensity of pain was assessed, using a linear pain analogue scale of 1–10.

After this, patients were reviewed weekly until full wound healing was achieved and again at 3 and 6 months postoperatively.

Results

One hundred and forty patients underwent one hundred and seventy procedures. There were 55 WRs, 53 SPs, and 62 combination procedures. The male:female ratio was approximately 2·7:1 and the age range was 9–54 years, with a mean age of 21 years (*Table 1*). Both age and sex were similarly distributed between the three groups (*Table 2*).

The lateral side of the nail was three times more commonly involved than the medial side. As regards aetiology, a history of

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Table 1 *Age and sex distribution of patients with ingrowing toenails*

			Decade of life						
	Number	Age range	1st	2nd	3rd	4th	5th	6th	Mean age
Males	102	12–48 years	0	70	21	9	2	0	20·0 years
Females	38	9–54 years	1	23	7	3	1	3	22·8 years
Total	140	9–54 years	1	93	28	12	3	3	21·1 years

Table 2 *Age and sex distributions of patients in the three treatment groups*

				Decade of life						
Treatment group	Total number	Males	Females	1st	2nd	3rd	4th	5th	6th	Mean age
WR	42	30	12	1	27	9	2	2	1	20·0 years
SP	45	35	10	0	30	8	5	1	1	21·4 years
WR/SP	53	37	16	0	36	11	5	0	1	20·8 years

WR, wedge resection, SP, segmental phenolization; WR/SP, wedge resection/segmental phenolization combination treatment

Table 3 *Postoperative pain duration of patients in the three treatment groups*

Treatment group	No pain	1–6 h	6–12 h	12–24 h	Over 24 h	Mean ± s.d.
WR	5	13	9	11	17	30·0 ± 37·6
SP	17	24	7	2	3	6·7 ± 13·0
WR/SP	19	21	10	9	3	9·4 ± 13·5

WR, wedge resection; SP, segmental phenolization; WR/SP, wedge resection/segmental phenolization combination treatment

Table 4 *Postoperative pain intensity of patients in the three treatment groups*

Treatment group	No pain LPAS 1	Mild pain LPAS 2,3,4	Moderate pain LPAS 5,6,7	Severe pain LPAS 8,9,10
WR	5	8	30	12
SP	17	18	17	1
WR/SP	19	20	19	4

LPAS, linear pain analogue scale; WR, wedge resection; SP, segmental phenolization; WR/SP, wedge resection/segmental phenolization combination treatment

improper nail trimming was identified in 108 cases (63·5 per cent), tight footwear in 85 (50 per cent), previous injury to the toe in 43 (25·3 per cent), and 69 cases occurred in active sport persons (40·6 per cent). Fifty-two cases (30·6 per cent) had had previous surgical procedures performed on the same affected side of the toenail (19 of the WR group, 17 of the SP group and 16 of the WR/SP group).

Postoperative pain duration

Pain duration in the SP and WR/SP groups was similar with no statistically significant difference between the treatment groups. However, both groups had significantly shorter pain duration postoperatively when compared with the WR group ($P<0{\cdot}001$ in both groups, Student's t test) (*Table 3*).

Postoperative pain intensity

Pain intensity in the three groups is shown in *Table 4*. Pain intensity was similar to pain duration in that there was no statistically significant difference between the SP and WR/SP groups and both SP and WR/SP were themselves less painful procedures than WR ($P<0{\cdot}001$ in SP group and $P<0{\cdot}005$ in WR/SP group, χ^2, 2×4 contingency tables).

Recurrence rates

At the end of the 6-month follow-up period there were 11 recurrences in the 170 procedures performed. Two patients were lost to follow-up, one in the WR group and one in the SP group. Recurrence was defined by the presence of nail growth on the affected side, whether or not symptomatic, i.e. an asymptomatic nail spike was considered a recurrence. There were seven recurrences in the WR group (13·0 per cent) and four recurrences in the SP group (7·7 per cent). There were no recurrences in the WR/SP group.

There was a statistically significant difference in the recurrence rate between WR/SP and WR groups ($P<0{\cdot}01$) and the WR/SP and SP groups ($P<0{\cdot}05$ Fisher's exact test). There was no statistically significant difference between the SP and WR groups.

Discussion

To date, the results following approaches other than WR and SP remain disappointing. Simple nail conservation treatment, such as the approach described by Lloyd-Davies and Brill[7], is easy to undertake but is time-consuming and requires a high degree of patient cooperation and a long period to achieve cure. As a result, a large number of patients (40 per cent) tend to default from this treatment. The failure rate is also high with recurrences being seen in 45 per cent of those treated. Nail strip and total nail avulsion similarly result in unacceptably high failure rates, reported to range from 64 to 86 per cent[8–10]. The use of cauterization, liquid nitrogen, cryotherapy and other chemical agents, such as silver nitrate, in nail bed ablation, also results in high recurrence rates, some approaching 45 per cent[11]. Total nail bed ablation by the Zadik procedure[12] is associated with considerable postoperative pain and with recurrence rates ranging from 16 to 28 per cent[8,9], with many patients, particularly young females, objecting to the ugly cosmetic result. The more radical procedure of amputation of the terminal part of the distal phalanx[13–15] is unnecessary, has an unacceptable cosmetic result and is rarely, if ever, performed nowadays.

This study has looked at a new approach to the treatment of ingrown toenails by combining WR with SP. This new treatment has been compared with the two widely used approaches of standard WR and of standard SP.

This study proves that this new combination treatment is successful, if judged by the lack of recurrence, showing significantly better results when compared with WR ($P<0{\cdot}01$)

and SP ($P<0{\cdot}05$). This may be explained by the effect of phenol in ablating what may potentially remain of the nail bed after the standard WR, and by the fact that tissue penetration by the phenol is more effective following debulking of the nail bed than with the standard SP.

Pain intensity after WR/SP was less than that after WR but compared favourably with that following SP, which remains the least traumatic of the available surgical procedures. For this reason it may still remain the procedure of choice in elderly patients with diabetes and peripheral vascular disease. The reason for the reduction in postoperative pain may be related to the effect of phenol on the sensory nerve endings. Undoubtedly WR, in expert hands using meticulous surgical technique, will produce good results, but in this new combination treatment the phenol corrects the inadequacy of total surgical removal of nail bed and, therefore, is of particular advantage in alleviating the need for surgical expertise, since the majority of these procedures are performed by junior staff. We believe that following WR/SP no recurrences should take place, regardless of operator experience.

The procedure can be carried out on an outpatient basis under local anaesthesia. The phenolization adds a mere 3 min to the operative time of WR and the extra cost of the phenol is negligible.

Blood pooling at the nail bed is undesirable and renders excision technically more difficult. It also dilutes the phenol to below its optimum concentration. Thus, it is important that a tourniquet is applied in all cases. The tourniquet also prevents the absorption into the circulation of the local anaesthetic agent, thus prolonging its effect.

The use of local anaesthesia by ring block should be routine in these procedures. The proper technique of ring block never fails to establish total anaesthesia to the toe. The use of combined short-acting lignocaine and long-acting bupivacaine as local anaesthetic agents has the advantage of providing a longer pain-free postoperative period (usually 3–4 h), without the delay in achieving anaesthesia. In our experience this was most satisfactory and we feel that its use should be encouraged. General anaesthesia is unnecessary and costly and carries a potential risk of complications; its use should be abandoned in these procedures.

In conclusion, we have demonstrated, in a well-controlled prospective study of the treatment of ingrown toenails, that recurrence rates can be reduced to very low and acceptable levels. We have shown that the WR/SP combination treatment is more successful than either WR or SP alone and, with regard to postoperative pain, is a less painful procedure than WR alone but compared favourably to SP alone. We conclude that this new combination treatment is a superior form of treatment for ingrowing toenails.

Acknowledgements

We would like to thank the staff in the Medical Records Department and the nursing staff of the Accident and Emergency Department in The Adelaide Hospital, Dublin, for their assistance in carrying out this study. We would also like to thank Mr Patrick Byrne for statistical analysis of the data and Miss Valerie Ingoldsby for preparation of the manuscript.

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Smooth muscle tumours of the digestive tract: report of 160 cases

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Of 160 patients seen in the period 1951–84 with smooth muscle tumours of the digestive tract, 71 proved to have leiomyomas, 87 had leiomyosarcomas and 2 had leiomyoblastomas. Tumour diameter was frequently greater in patients with leiomyosarcoma. The surgical mortality was 2·8 per cent after treatment of leiomyoma and 10·3 per cent after treatment of leiomyosarcoma. After resection of leiomyosarcoma the 2-year survival rate was 86 per cent and the 5-year survival rate was 43 per cent. The only hope of cure of these malignant lesions lies in surgical resection but, even when the lesion is incurable, resection may allow worthwhile palliation.

Keywords: Leiomyoma, leiomyosarcoma, digestive tract

Smooth muscle tumours of the digestive tract, both benign and malignant, are generally assumed to be rare. This study was undertaken to analyse 160 cases of smooth muscle tumours of the digestive tract in terms of clinical presentation, histopathological characteristics, differential diagnosis, treatment and results.

Patients and methods

A retrospective search of the records of Zhongshan Hospital, Shanghai Medical University revealed 160 patients in whom a diagnosis of leiomyoma, leiomyosarcoma or leiomyoblastoma of the digestive tract was made in the period 1951–84. The records of these patients were reviewed. A total of 11 patients died within 30 days of operation, 14 patients were lost to follow-up, and the remaining 135 patients were followed by means of questionnaire. The pathological sections of material from these patients were reviewed. On the basis of tumour size, cellularity, cellular atypia, mitoses and follow-up results, criteria for the diagnosis of leiomyosarcoma were revised, and all patients were reclassified.

Results

In this series of patients, 107 were male and 53 female. The age range was 17–73 years, with a mean of 36·3 years in patients with oesophageal leiomyoma, 49·4 years in gastrointestinal leiomyoma and 50·8 years in gastrointestinal leiomyosarcoma.

The chief symptoms in the 28 patients with oesophageal leiomyoma were dysphagia (26 cases) and substernal discomfort or pain (17 cases). The clinical presentation in the remaining 131 patients with smooth muscle tumours of the gastrointestinal tract is shown in *Table 1*.

Smooth muscle tumours could be classified as extraluminal in 81 cases (50·6 per cent, *Figure 1*), intraluminal in 45 cases (28·2 per cent (*Figure 2*), transmural in 17 (10·6 per cent) and intramural in 17 (10·6 per cent). The mean diameter was 3·4 ± 2 cm (range 0·7–8·5 cm) in the case of oesophageal leiomyoma, 4·7 ± 2 cm (range 1·5 ± 9·0 cm) in gastrointestinal leiomyoma and 10 ± 5·3 cm (range 1·5–25·0 cm) in gastrointestinal leiomyosarcoma. Only in three cases (7 per cent) of gastrointestinal leiomyoma was the diameter greater than 8 cm, and in no case was it greater than 10 cm. In 51 cases (59·3 per cent) of gastrointestinal leiomyosarcoma the diameter was greater than 8 cm, while in 36 cases (41·9 per cent) it was greater than 10 cm. The site , nature and mean diameter of the 160 tumours are shown in *Table 2*.

The incidence of haemorrhage, central necrosis (*Figure 3*) and cystic degeneration (*Figure 1*) was 32·6 per cent (14/43), 53·5 per cent (23/43) and 69·8 per cent (30/43) respectively in the gastrointestinal leiomyomas and 65·1 per cent (56/86), 75·6 per cent (65/86) and 86 per cent (74/86) respectively in the gastrointestinal leiomyosarcomas. There was often a small ulcer

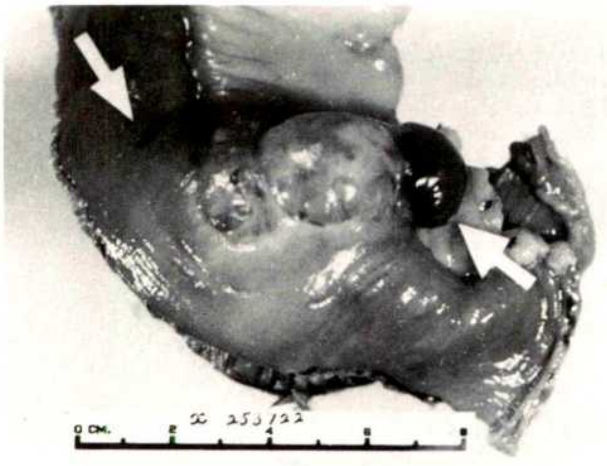

Figure 1 *Leiomyoma of the jejunum (extraluminal type) with multiple areas of cystic degeneration*

Table 1 *Clinical presentation of 131 patients with smooth muscle tumours of the gastrointestinal tract*

Symptoms and signs	Leiomyoma	Leiomyosarcoma	Leiomyoblastoma	Total (%)
Abdominal or pelvic mass	12	60		72 (55)
Gastrointestinal bleeding	31	36	2	69 (52·7)
Abdominal pain	22	36	2	60 (45·8)
Fever	4	29		33 (25·2)
Partial obstruction	4	5		9 (6·9)
Acute abdomen*	5	7		12 (9·2)

* Acute abdomen included haemoperitoneum (6 cases), intussusception (3 cases), infection with abscess formation (2 cases) and volvulus (1 case)

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crater on the mucosal surface (*Figure 2*), sometimes with a sinus leading to the area of central necrosis.

In 40 cases, 1–5 mitoses per 25 high-power fields were found: such tumours were considered to be low-grade malignant leiomyosarcomas. In 42 cases more than five mitoses were seen; they were diagnosed as leiomyosarcomas of high-grade malignancy. Five tumours, although morphologically benign, exhibited biological behaviour which was apparently malignant; they were classified as leiomyosarcoma.

At operation, nine patients (10·5 per cent) with leiomyosarcoma were found to have peritoneal implantations, six patients (7 per cent) had liver metastases and five patients (5·8 per cent) had lymph node spread.

The treatment and results obtained in the patients with leiomyoma and leiomyosarcoma are shown in *Tables 3* and *4*, respectively. The 2-year survival rate of patients with leiomyosarcoma after resection was 85·5 per cent (53/62) and the 5-year survival rate was 43·1 per cent (22/51). Two patients with leiomyoblastoma of the stomach were dealt with by local excision and have remained well for 5 years 9 months and 6 years 8 months, respectively.

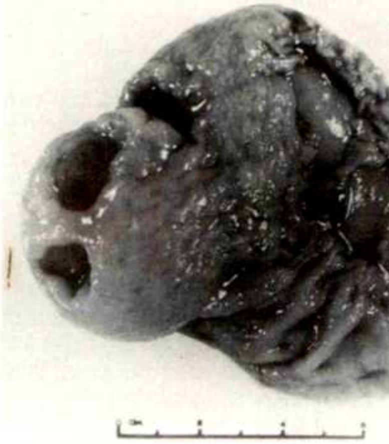

Figure 2 *Leiomyoma of the stomach (intraluminal type), showing two ulcer craters*

Table 2 *Site and mean diameter of tumours in 160 cases of smooth muscle tumour*

	Leiomyoma		Leiomyosarcoma		Leio-myoblastoma	
Site	No. of cases	Mean diameter (cm)	No. of cases	Mean diameter (cm)	No. of cases	Mean diameter (cm)
Oesophagus	28	3·4	1	1·8		
Stomach	21	4·6	34	9·8	2	4·2
Duodenum	7	3·8	11	7·8		
Jejunum	7	5	14	11·6		
Ileum	4	5	12	10·7		
Colon			3	10·6		
Rectum	4	6	12	7·8		
Total	71		87		2	

Discussion

Smooth muscle tumours of the digestive tract, both benign and malignant, are relatively rare. In our hospital, leiomyoma comprised about 25·3 per cent of the benign tumours of the digestive tract, while leiomyosarcoma accounted for 0·98 per cent of the malignant tumours in the digestive tract. In our series, the most frequent site of tumour formation was the stomach (57 cases, 35·6 per cent): there were 21 cases of leiomyoma, 34 cases of leiomyosarcoma and 2 cases of leiomyoblastoma. The next sites of predilection were the oesophagus (29 cases, 18·1 per cent) and jejunum (21 cases, 13·1 per cent). The overwhelming majority of the smooth muscle tumours in the oesophagus were benign, being malignant in only one case, whereas those in the stomach were largely malignant.

According to our data, extraluminal expansion was by far the more common mode of growth, so that patients remained asyptomatic in the early stages. Tumours usually presented because of bleeding, obstruction or development of the acute abdomen, and when an abdominal or pelvic mass was palpable.

Smooth muscle tumours of the oesophagus and stomach can be discovered relatively easily by fibreoptic endoscopy and barium meal examination, whereas those of the small intestine are often difficult to diagnose. For the latter the string test, hypotonic small bowel series and selective arteriography may be of value.

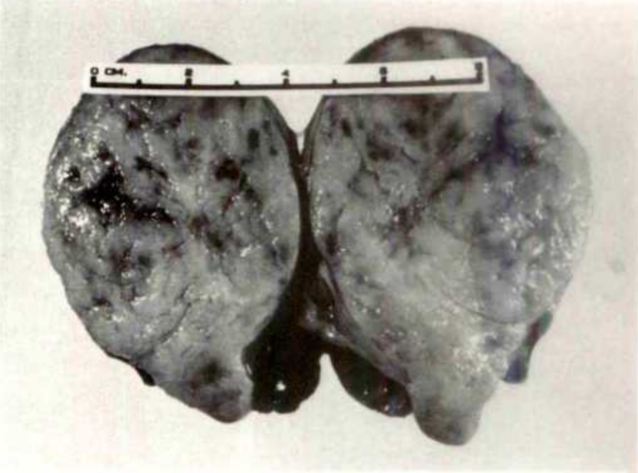

Figure 3 *Leiomyosarcoma of the stomach with multiple foci of haemorrhage and necrosis*

Table 3 *Treatment and results in 71 cases of leiomyoma*

Site	Enucleation	Resection	Surgical mortality (%)	Lost to follow-up	Survival		
					<5 years	5–10 years	>10 years
Oesophagus	25	3		2	5	8	13
Stomach		21	1 (4·8)	1	5	3	11
Duodenum	1	6	1 (14·3)		3	2	1
Jejunum		7			4	1	2
Ileum		4		2		1	1
Rectum	1	3			1		3
Total	27	44	2 (2·8)	5	18	15	31

Table 4 *The treatment and results in 87 cases of leiomyosarcoma*

Site	Biopsy only	Enucleation	Radical resection	Surgical mortality (%)	Lost to follow-up	Late mortality			Survival with disease (recurrence or metastases)	Survival with no evident disease		
						<2 years	2–5 years	>5 years		2–5 years	6–10 years	>10 years
Oesophagus			1							1		
Stomach	4		30	3 (8·8)	5	6	4	2	2	6	5	1
Duodenum	1		10	1 (9·1)		2	5	2	1			
Jejunum			14	3 (21·4)	1	3	4	2	1			
Ileum			12		1	2	6	1	1		1	
Colon	1		2	1 (33·3)	1	1						
Rectum	1	2	9	1 (8·3)	1	2	1	1	1	2		3
Total	7	2	78	9 (10·3)	9	16	20	8	6	9	6	4

Haemorrhage, central necrosis, and cystic degeneration were often encountered in large tumours, and can produce massive haemorrhage into the gastrointestinal tract. Smooth muscle tumours should therefore be considered in the differential diagnosis of gastrointestinal tract haemorrhage of undetermined cause. The tumours may also cause obstruction, and even give rise to acute abdominal symptoms and signs when they rupture, become intussuscepted or secondarily infected.

The differential diagnosis between benign and malignant smooth muscle tumours is sometimes quite difficult. Most pathologists have suggested that tumour size and the number of mitoses are useful criteria. Golden and Stout[1] pointed out that when two or more mitoses are seen in one high-power field, the tumour definitely should be classified as malignant. Ranchod[2] suggested that the number of mitoses found is the most useful criterion: gastrointestinal smooth muscle tumours with five or more mitoses/10 high-power-fields should be diagnosed as leiomyosarcoma. Tumour cell necrosis and aggressive behaviour were closely associated when mitoses were infrequent. If the requisite number of mitoses, or tumour cell necrosis, are absent, tumour size, cellularity and cellular atypia may be helpful parameters when assessed together. Intestinal smooth muscle tumours which are cellular or show cellular atypia should be viewed with suspicion, especially if they are larger than 5 cm in diameter. On the basis of our data, malignancy should be suspected strongly when the diameter of the tumour is greater than 8 cm as there is a statistically significant difference between gastrointestinal leiomyoma and leiomyosarcoma in this regard ($P<0{\cdot}05$). If 1–5 mitoses are seen within 25 high-power-fields, the tumour is a low-grade malignant leiomyosarcoma; if more than five mitoses are seen, then the tumour is regarded as a leiomyosarcoma of higher-grade malignancy. As the differences between the two above groups were not statistically significant, haemorrhage, central necrosis and cystic degeneration are not a reliable means of distinguishing benign from malignant tumours.

Malignant smooth muscle tumours are usually radioresistant and insensitive to chemotherapeutic agents: the only hope of cure lies in surgical resection. Because leiomyosarcomas are usually low-grade malignant, the primary tumour should be resected whenever possible, even though it has already metastasized. Local recurrences should be removed, and even patients with repeated recurrences should not be abandoned without trying as hard as possible to remove the tumour.

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Peptic ulcer surgery and colorectal cancer risk

Sir

We concur with the recently published paper by Toftgaard (*Br J Surg* 1987; **74**: 573–5) and recent letter by Houghton and Mortensen (*Br J Surg* 1987; **74**: 1066) that there is no statistically significant association between gastric surgery for benign peptic ulcer disease and the subsequent development of colorectal cancer (CRC). We examined, *inter alia*, the associations between previous surgery for benign peptic ulcer disease and CRC as part of a large, comprehensive, population-based study of CRC incidence, aetiology and survival (The Melbourne Colorectal Cancer Study[1]). Previous peptic ulcer surgery was noted in 11 of 715 CRC cases and in 17 of 727 age and sex matched community controls ($\chi_1^2 = 0{\cdot}8$, $P > 0{\cdot}05$). The three studies above are not consistent with the earlier report of Bundred and colleagues[2] who found that more patients with CRC had previous gastric surgery for benign peptic ulcer disease than matched hospital controls ($P < 0{\cdot}05$). The relatively small study numbers of CRC cases (289) and/or some unrecognized form of selection bias may have accounted for the differences noted by Bundred and colleagues—differences which were not seen in the other three studies.

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Pre-operative assessment of fitness score

Sir

I would like to raise certain points regarding the Playforth *et al.* study (*Br J Surg* 1987; **74**. 890–2).

Firstly, there was no mention of the 'technical proficiency' of the anaesthetist involved in the operation. Anaesthetic complications can affect the outcome of the operation, e.g. peroperative hypotension[1]. Some anaesthetic techniques can reduce the incidence of deep vein thrombosis[2].

Secondly, some of the factors in the pre-operative assessment mentioned in the study might reflect poor preparation of patients for major elective abdominal surgery, e.g. Hb $< 10\,\mathrm{g\,dl}^{-1}$ or myocardial infarction within 6 months The latter has an incidence of postoperative re-infarction of 15–40 per cent with mortality rate of 50 per cent[3]. Patients should be at their optimal condition before the operation Invasive haemodynamic monitoring with aggressive management at the per- and postoperative periods reduce the incidence of cardiovascular complications dramatically[4].

Thirdly, it is unclear whether the assessment factors are additive or not.

Finally, according to *Table 3*, there were three emergency deaths with scores less than six. But according to *Table 4*, there was only one emergency case (ruptured aortic aneurysm)!

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4. Rao TLK, El-Etr AA. Myocardial reinfarction following anaesthesia in patients with recent infarction *Anaesthesia and Analgesia* 1981; **60**: 271–2.

Hormonal manipulation in the treatment of pancreatic carcinoma

Sir

I would like to reply to the comments of Messrs Crowson and Fielding (*Br J Surg* 1987; **74**: 1067) on my leading article on hormonal manipulation for the treatment of pancreatic carcinoma (*Br J Surg* 1987; **74**· 441–2).

I was undoubtedly at fault for not mentioning their article on a phase II trial using tamoxifen demonstrating a negative effect I knew of Mr Fielding's work, but neither myself nor the medical department of ICI could find his article and wrongly presumed it unpublished. However, I must take serious exception to their conclusion that the article was inaccurate, based solely on the absence of their report and the lack of objective assessment of response to treatment by the studies discussed. The three other reports of tamoxifen therapy cited did show an increase in the length of survival which, in a disease with such a short survival, is a rather better endpoint than radiological criteria.

What appeared to escape their attention was the main thrust of the paper, which is that both the experimental work and the accumulating clinical evidence using both tamoxifen and a luteinizing hormone-releasing hormone antagonist, is highly suggestive that hormone therapy may have a part to play in the treatment of pancreatic carcinoma. This is given further support for yet another study demonstrating a positive effect for tamoxifen therapy, from Wong *et al.*[1] in 24 patients, 3 living for longer than 2 years.

It is quite obvious that the effects of tamoxifen therapy, in the four positive reports published so far, is small. However, it is extremely important in a disease with such an appalling prognosis that this effect is noted and that further clinical trials of hormone therapy with other agents is encouraged and not allowed to drift into obscurity based upon the one published uncontrolled trial with few patients demonstrating a negative effect.

I am guardedly optimistic and I hope my leading article will have given encouragement to clinicians to perform further clinical trials; after all, at present we have nothing else to offer these patients

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1. Wong A, Chan A, Arthur K. Tamoxifen therapy in unresectable adenocarcinoma of the pancreas. *Cancer Treatment Reports* 1987, **71**. 7–8.

'Button hole' incisional hernia

Sir

Krukowski and Matheson (*Br J Surg* 1987; **74**: 824–5) drew our attention to the existence of hernias, often multiple, lateral to midline incisions, due to defects created by continuous non-absorbable sutures. I have encountered three such hernias, and have operated on two of them.

Two of these patients had had radio-opaque markers attached to each leaf of the aponeurosis during operation and these had shown no separation when the abdomen was X-rayed a month later[1]. It is clear that this type of para-incisional hernia is caused not by defective healing but by a 'cheese wire' effect of continuous non-absorbable sutures in the aponeurosis.

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1. Playforth MJ, Sauven PD, Evans M. Pollock AV The prediction of incisional hernias by radio-opaque markers. *Ann Roy Coll Surg Engl* 1986; **68**: 82–4.

'Skew flap' below-knee amputation

Sir

Mr Harrison and his colleagues (*Br J Surg* 1987, **74**. 930–1) suggest that the skew flap amputation gives superior results to the long posterior flap below knee amputation. This conclusion is not supported by the data they present. Patients in the two groups have clearly experienced totally different standards of vascular surgical care which predictably has affected primary healing and complication rates. All the skew flap amputations were performed between 1983 and 1986, whereas 70 per cent of the long posterior flap amputations were performed at a time when the total number of amputations was almost 50 per cent higher. A reduction in the numbers of amputations by a third when other centres have consistently reported a substantial increase[1–3] suggests a qualitative change in vascular surgical practice in Derby. Further evidence of a surgical reformation is provided by the fact that more than one in three patients with skew flap amputations had previously undergone a vascular surgical operation other than sympathectomy, compared with only one in twelve long posterior flap amputees.

A retrospective audit of our own experience up to 1983[3] revealed that only 38 per cent of amputations were at the below knee level. Since February 1986 a deliberate policy of performing amputation below the knee whenever possible has been adopted. The implementation of this plan was accompanied by the refinement and standardization of our surgical technique for long posterior flap amputations. Progress has been monitored by continuous critical audit of performance and results This strategy has resulted in 67 per cent of the 96 primary lower limb amputations in the last 19 months being at the below knee level.

Our experience suggests that when results are suboptimal, substantial improvements in performance can be achieved by the recognition of a problem, a determination to solve it, and continuous monitoring of progress.

While Harrison *et al.* are to be congratulated for increasing the proportions of below knee amputations performed from 23·7 per cent to 41·5 per cent, we believe they are incorrect in attributing this improvement to the use of the skew flap amputation. Much better results can be achieved with the long posterior flap amputation.

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1. Liedberg E, Personn BM Increased incidence of lower limb amputation for arterial occlusive disease. *Acta Orthop Scand* 1983; **54**: 230–4.
2. Harris PL, Read F, Fardley A, Charlesworth D, Wakefield J, Sellwood RA. The fate of elderly amputees. *Br J Surg* 1974, **61**. 665–8.
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Authors' reply

Sir

In reply to the letter of McWhinnie *et al.* we should like to re-iterate that our data clearly suggest (although do not prove) that the skew flap amputation gives superior results. Whilst the skew flap amputations were performed in the latter time period of the study they are in every other way comparable, and there are no statistically significant differences between the groups with respect to previous vascular surgery.

Whilst we applaud their advancement of surgical audit to improve results it is clear that we also have seen a steady increase in the rate of below the knee amputations performed in Derby (as opposed to a reduction noted in their paper of 1986).

They are not really in a position to make their final remark, that much better results can be obtained with the long posterior flap, since they have not compared it with the skew flap, as we have.

J. D. Harrison
K. G. Callum

Radionuclide ejection fraction

Sir

Encouraged by the results of Mosley *et al* (*Br J Surg* 1985; **72**: 886) we have measured the radionuclide left ventricular ejection fraction (EF) of 23 patients undergoing aortic surgery (15 for abdominal aortic aneurysm, 8 for occlusive disease) Our results differ from those of the authors' in that 2 cardiac deaths occurred in the group with 'normal' left ventricular function (> 60 per cent).

A 77-year-old lady with an EF of 71 per cent suffered a perioperative myocardial infarct, during an otherwise uneventful repair of an aneurysm, and died on the second postoperative day. A post-mortem examination revealed severe triple vessel coronary artery disease with a recent occlusion of the left anterior descending coronary artery. A 66-year-old man also with an EF of 71 per cent developed intractable left ventricular failure after an aortobifemoral graft and died on the fifth postoperative day. Again post-mortem examination showed severe triple vessel coronary artery disease with recent coronary occlusion and myocardial infarction. These deaths occurred despite normal left ventricular ejection fraction, uneventful surgery and perioperative Swan–Ganz catheterization.

The assessment of left ventricular function by radionuclide angiography identifies those patients with poor function at rest but does not necessarily indicate how patients with normal function will respond to stress. The addition of exercise, though sometimes difficult in patients with peripheral vascular disease, may help to identify those patients who deteriorate under stress but is technically difficult to combine with radionuclide angiography. As the authors mention, aortic cross clamping causes a rise in systemic vascular resistance and myocardial wall tension which reduces coronary artery blood flow and myocardial oxygen supply. In those patients with a precarious coronary artery circulation this may cause perioperative myocardial infarction.

The intravenous administration of dipyridamole during thallium scanning (DTS) causes coronary artery vasodilation which mimicks the effect of exercise and can identify haemodynamically significant coronary artery disease Cutler *et al.* found that the absence of thallium redistribution after DTS was associated with no perioperative myocardial infarction after abdominal aortic surgery, whereas an abnormal scan was associated with a 26 per cent perioperative infarct rate[1].

We believe the radionuclide EF is a useful investigation to identify those patients with poor left ventricular function who require close perioperative monitoring. However a normal result does not exclude significant coronary artery disease. The addition of DTS should identify those patients who might benefit from myocardial revascularization before abdominal aortic surgery

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1. Cutler BS, Leppo JA. Dipyridamole thallium 201 Scintigraphy to detect coronary artery disease before abdominal aortic surgery. *J Vasc Surg* 1987; **5**: 91–100.

Wound healing

Sir

We are pleased to see the results reported by D E. M. Taylor, J. S. Whamond, and J. E. Penhallow (*Br J Surg* 1987; **74**: 316–19), who have confirmed McGinn's work on the effect of oligaemia on wound healing. However, we feel that the authors have made conclusions about mechanisms which are not warranted by the data. We specifically question the conclusion that 'the effect of compensated oligaemia . . . appears to be a specific increase in collagen turnover with the increase in reabsorption exceeding that in synthesis ' We do not contest the result that 21 days after injury tensile strength of wounds in animals with 'compensated oligaemia' was lower and that uptake of hydroxyproline was higher. Without reference to the cycle of wound healing their hypothesis appears correct. However, conversion of proline to hydroxyproline follows a curve, from low levels at injury to high levels in several days and descending thereafter The higher hydroxyproline formation at 21 days in the compensated oligaemic group, therefore, may merely mean that healing has been delayed a few days. Since blood was removed from these animals only at the time of wounding, one would expect the oligaemia to have been compensated within a few days. Therefore, the most likely conclusion is that wound healing in the oligaemic animals was retarded at the very beginning, has reached its peak, and has just not fallen quite as far as the normals have at this date.

Our findings, showing that collagen synthesis in wounds is diminished by oligaemia, hyperviscosity and hypoxia, are consistent with the latter hypothesis. To the best of our knowledge no one has yet shown an effect of oligaemia on collagen lysis.

In short, we cannot agree with these authors' conclusion that lysis is increased by 'compensated oligaemia' until they can prove to us that hydroxyproline incorporation in their model is not descending before the time of their measurement. They suggest in the final sentence of the paper that they are going to extend their studies to cover this point. We eagerly await the result

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Controlled trial of occlusive dressing in healing chronic venous ulcers

Sir

The recent paper by Backhouse and colleagues (*Br J Surg* 1987; **74**: 626–7) serves to re-emphasize the critical importance of adequate compression bandaging in the management of chronic venous ulcers and the authors are to be commended on achieving a cure rate of nearly 80 per cent. It should, however, be pointed out that, for very good reasons, only ulcers $< 10\ \text{cm}^2$ were included in the trial and so, given the degree of attention that the patients received and the four-layered compression bandaging technique, it was hardly surprising that no significant difference in healing rates was detected between the treatment groups. Unfortunately, the majority of leg ulcer patients do not receive this degree of expert supervision and 80 per cent never have the benefit of hospital referral[1]. Moreover, most of the materials used in this trial are not on the Drug Tariff and are, therefore, unavailable for use in the community.

Their main conclusion, however, that the use of Granuflex dressings is not justified on the basis of cost alone is not, I feel, a valid one The unit cost of the primary dressing represents only a small proportion of the total costs of treatment. In terms of unit cost, Granuflex is, in fact, cheaper than almost any of the newer dressing materials now on the market. At no point do the authors give the actual costs of other materials used, which would have been of considerable interest in a paper which seems to suggest that cost is the major deciding factor in choice of primary dressing material There are, however, other factors that need to be considered, such as patient preference, important in a condition in which patient compliance with treatment is notoriously poor, as well as propensity for skin sensitization.

We have recently completed large scale, prospective, randomized, comparative trials of Granuflex in the community using paraffin gauze, paste bandages and NA dressings as the comparators and it is hoped that these data will be published soon. The results of these trials, which included ulcers of all sizes (and most were $> 10\ \text{cm}^2$) do not accord with those of these authors in either efficacy or cost per unit area of healing achieved, which is probably the only valid basis for comparing cost effectiveness in this condition.

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1 Callam MJ, Ruckley CV, Harper DR, Dale JJ. Chronic ulceration of the leg extent of the problem and the provision of care. *Br Med J* 1985, **290**: 1855–6.

Authors' reply

Sir

We are grateful to Mr Weston-Davies for stressing the importance of good compression in healing venous ulcers, in our study, the combination of good compression and Granuflex dressings produced the best healing rate yet reported for any study involving Granuflex. We would also endorse his comments that materials necessary for a 'proven system' of high pressure bandaging should be available on the Drug Tariff for use in the community as it would not be possible for the majority of patients to regularly attend outpatients. Our plan is to introduce community venous ulcer clinics with district nurses trained in the safe application of sustained compression bandage systems

We apologize for commenting on the cost of Granuflex without giving the appropriate data: Granuflex costs £1.60 per $10\ \text{cm}^2$ compared with 16p for simple NA dressings[1]. However, this pales to insignificance compared with the overall cost of £5200 per patient per year when repeatedly dressed in the community[2]. We did not in fact state that the use of Granuflex is not justified on the basis of cost alone, although cost would always be a consideration.

In our study, compliance was excellent and we attribute this to the comfort of the bandages together with the absence of any skin sensitization to either Granuflex or simple NA dressings. Probably the most important factor in compliance is that the patients should be able to see consistent ulcer healing each week.

We clearly cannot comment on Mr Weston-Davies' unpublished data but look forward to seeing the details in print.

C. M. Backhouse
S. D. Blair
C. N. McCollum

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1 Dressings for leg ulcers *Drugs and Therapeutics Bulletin* 1986, **24**(3): 9–12.
2. Pottle E Trial of a dressing for non-healed ulcers. *Nursing Times* 1987; **83**· 54–8.

Publication lag times in surgical journals

Sir

The letter from Mr Mathie and Mr Jaffe (*Br J Surg* 1987; **74**. 1188) is an important introduction to a vexing problem As always the definition of terms and objectives is important before we begin apportioning responsibility which the authors wisely do not. Time from submission to publication ('publication speed' in Mathie and Jaffe's terminology) is composed of (a) time between receipt and processing in the editorial office; (b) time for editorial plus peer review; (c) time for editorial re-review in the light of referees' reports (ominously called at the *British Medical Journal* the 'hanging' committee); and (d) time between acceptance and publication. Any good journal office will keep the first three to a minimum, and computers do help, but it can never reduce it to what many authors think should be the appropriate figure—zero. We find that it takes about 6 weeks to 2 months to get through this process and we are rigorous in discarding referees who cannot return manuscripts quickly (few I am glad to say) The last component (d) is often less easy to understand It is made up of (i) the importance editors attach to early publication; (ii) the need to group publications so as to make an attractive journal, (iii) time taken in checking details with authors, and (iv) the need to have a bank of copy so as to smooth out the flow of accepted material and not have the editorial nightmare of being unable to fill an issue The interaction of these factors is extremely variable but accounts for the range of 2–8 months quoted for the acceptance and publication time of the BJS

All authors like to get into print quickly. Putting aside priority, which is a very difficult issue but probably matters little in the long run except to one's *amour propre*, we recognize the importance that publications have to career advancement. For this purpose we believe that if the paper can be entered on a c.v. as 'in press' then this is sufficient to impress, one way or another, the selection panel for the author's next job. Hence we lay stress on keeping (a), (b) and (c) to a minimum though we would be further helped in this task—and here I write on behalf of my editors—if authors would conform to our instructions; submit clear, unambiguous prose, and finally keep their manuscripts short.

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Biliary lithiasis in the elderly

Sir

The recent paper by Duron and colleagues (*Br J Surg* 1987; **74**: 848–9) presents an interesting view of the management of elderly high-risk patients with gallstones. The authors' message is that patients with suspected common bile duct (CBD) stones should undergo endoscopic sphincterotomy (ES) followed shortly afterwards by surgery; all other patients should be operated upon. Yet the overall mortality in this series of 64 patients was 11 per cent of whom only 28 (44 per cent) had CBD stones—a subgroup known to have an increased mortality. Furthermore, it is difficult to justify undertaking ES in the absence of any CBD stones, as occurred in four cases in this series.

There is another strategy which ought to be considered[1]. High-risk patients with suspected CBD stones should undergo endoscopic retrograde cholangiopancreatography (ERCP); ES with active CBD stone extraction should only be undertaken if confirmed at ERCP. Surgery need not be undertaken automatically to remove the gallbladder. Other high risk patients may be managed conservatively. Only about 10 per cent of patients who undergo ES will develop gallbladder complications[2,3]. These patients, as well as those without CBD stones, who have problems such as empyema of the gallbladder may be managed by percutaneous transhepatic gallbladder decompression[4,5]. Gallstones may be subsequently treated by direct dissolution with chemical agents[6,7], perhaps in combination with extracorporeal shock wave lithotripsy[8].

The aim must be to reduce the mortality from biliary lithiasis to something approaching 0 per cent. Whereas surgery will continue to have a dominant role, progress in the management of these high-risk cases can only be achieved with the wider user of non-operative techniques

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1. Neoptolemos JP, Davidson BR, Shaw DE, Lloyd D, Carr-Locke DL, Fossard DP. Study of common bile duct exploration and endoscopic sphincterotomy in a consecutive series of 438 patients. *Br J Surg* 1987; **74**: 916–21.
2. Escourou J, Cordova JA, Lazorthes F, Frexivos J, Ribet A. Early and late complications after endoscopic sphincterotomy for biliary lithiasis with and without the gallbladder in situ. *Gut* 1984; **25**: 598–602.
3. Davidson BR, Neoptolemos JP, Carr-Locke DL. Endoscopic sphincterotomy for common bile duct calculi in patients with gallbladder in situ considered unfit for surgery. *Gut* 1988; **29** (in press).
4. Radder RW Ultrasonically guided percutaneous catheter drainage for gallbladder empyema. *Diagn Imaging* 1980; **49**: 330–3.
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7. Neoptolemos JP, Hofmann AF, Moossa AR. Chemical treatment of stones in the biliary tree *Br J Surg* 1986; **73**: 515–24
8. Saufrbruch T, Delius M, Paumsartner G *et al.* Fragmentation of gallstones by extracorporeal shock waves *N Engl J Med* 1986; **314**. 818–22.

Review of a hospital experience of breast abscesses

Sir

We were interested in the review of a hospital experience of abscesses by J. H. Scholefield, J. L. Duncan and K Rogers (*Br J Surg* 1987; **74**: 469–70). Our recent experience suggests that for small abscesses ultrasound guided needle aspiration is a suitable alternative to incision and drainage. A 14-year-old girl presented to us with an enlarged and painful right breast swelling for 2 days which did not respond to antibiotic treatment On examination an abscess, 3 cm in diameter, was found beneath her right nipple. Ultrasound examination confirmed the location and size of the abscess and needle aspiration under local anaesthesia yielded several millilitres of thick green pus. Her symptoms were relieved and after a further course of flucloxacillin all signs of inflammation subsided and she remained asymptomatic on follow-up 1 month later. Her breast remained unscathed of surgical scars.

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Book reviews

Colour Atlas of Head and Neck Surgery

J. Shah. 258 × 315 mm. Pp. 256. Illustrated. 1987. London: Wolfe Medical Publications. £75.00.

Many surgeons will be familiar with the *Colour Atlas* series produced by Wolfe Medical Publications and I am pleased to say that this new addition by Jatin Shah keeps up with the generally high standards of the series. In this first volume on head and neck surgery he covers various operative techniques involving the face, skull, and neck. In addition to the expected details of minor and major operative procedures, there is an opening chapter covering the operating room requirements and anaesthesia for head and neck surgery. The text is surprisingly comprehensive bearing in mind that this is primarily intended as a colour atlas and, where necessary, details of pre-operative assessment and treatment planning are also given.

The standard of colour photography is on the whole high and, as the photographs were taken by the author himself during the procedures, there is good continuity and the surgeon's field of view in each operation. There is a criticism, which is faced by most colour atlases, that, on a number of occasions where large operative fields are shown, accompanying line diagrams would add considerably to the clarification. A second volume is expected in the near future by the same author covering the remaining aspects of head and neck surgery, including the larynx, pharynx, thyroid gland and reconstructive procedures. If the same standard is maintained then this will prove to be an excellent two volume set for all those working in this complex and demanding specialty.

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Essentials of Surgery

D. C. Sabiston. 220 × 283 mm. Pp. 1207. Illustrated. 1987. Philadelphia. W. B. Saunders. £25.00.

Visitors from the UK to the major undergraduate teaching hospitals in the USA are impressed by many things—but one of the most impressive is the phenomenon of the American medical student. Older than ours, it is true, but characterized by enormous dedication, hard work, and encyclopaedic knowledge. Alongside this prodigy is the phenomenon of the American student textbooks, which are correspondingly more comprehensive than the slim volumes sported by our own surgical dressers.

To other well-known works is now added this new volume edited by David Sabiston of Duke University School of Medicine. It is based on his well-known *Textbook of Surgery* and is presented as a more concise volume designed specifically for medical students. *Essentials of Surgery* is still a massive tome, which rests heavily on the knees. It has 90 contributors, the great majority from the USA, who cover the whole range of surgery including ENT, but not opthalmology. Gynaecology is dealt with in a brief chapter of 24 pages and I suspect that the students will need more than this. Each major topic includes a historical introduction, a full consideration of its scientific basis and a pertinent bibliography, as well as a list of selected recommended references.

Certainly this is a major contribution to surgical teaching. In this country, it will be welcomed by postgraduate trainees rather than medical students. However, perhaps the latter will be encouraged by the succinct text and copious illustrations of *Essentials of Surgery* to use it as a mine of information.

H. Ellis

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Cutaneous Melanoma

U. Veronesi. 155 × 235 mm. Pp. 693. Illustrated. 1987. Ontario. Academic Press Inc. Harcourt Brace Jovanovich. £40.00

One hundred and fifty invited papers given at the First International Conference on skin melanoma in Venice in May 1985 provide a comprehensive coverage of the scientific and biological aspects of melanoma, including pathology, epidemiology and immunology. It is well up-to-date for a major publication, with references up to 1985 included. Adjuvant therapy (including limb perfusion) is dealt with but there is little on surgical aspects—less than 20 out of 700 pages deal with the management of primary melanoma or lymph node disease and surgical technique or surgical palliation gets no mention. In short, it is a useful summary of present day knowledge of non-surgical aspects of melanoma, particularly as seen by those who are recognized as authorities on the subject. It needs to be used in association with the book of abstracts of proffered papers, distributed at the conference—sometimes the proffered papers reflect the advancing edge of a subject as much as the invited expert reviews.

L. E. Hughes

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University of Wales College of Medicine
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The Italian Journal of Paediatric Surgical Sciences

214 × 272 mm. No. 0 October 1986. Naples. Associazione Cultori Scienze, Chirurgiche Pediatriche.

A new journal has appeared on the paediatric surgical scene; the first issue was published in October 1986. The journal will be published in English because, as the editors point out, scientific papers published in the Italian language receive very sparse international readership. This must be exasperating for the Italians and they are to be congratulated for their willingness to come to grips with the inexorable spread of English as the world's international language.

It is intended that the journal will include articles on general paediatric surgical topics as well as on matters of interest to the system specialists working in the paediatric age group. This is reflected in the presence in the first issue of an article on the surgical closure of patent ductus arteriosus in low birth weight premature infants with severe respiratory distress syndrome.

One particuarly pleasing feature of the first issue is a dedication to Professor Franco Soave, one of the founders of paediatric surgery in Italy and a leading figure in the field internationally. His contribution to the surgical treatment of Hirschsprung's disease by the endorectal pull-through technique was a major landmark in the effort to improve operative results and is currently used by many paediatric surgeons throughout the world. He was a charming and friendly man and his death was a sad loss to all who knew him personally.

The standard of the editorial and the two articles printed in the first issue is excellent. The data are clearly presented, results concisely described and justifiable conclusions drawn. If the editors can maintain this standard the journal deserves to be a success.

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Notices and announcements

20–21 February 1988
First International Congress of the North American Society of Phlebology
San Diego, California, USA
Information: Helane Fronek MD, 3051 Cranbrook Court, La Jolla, California 92037, USA

3 March 1988
Head Injuries in the District General Hospital (Practical Management)
Birmingham, UK
Information: Mr C. H. A. Meyer, Department of Neurosurgery, Midland Centre for Neurosurgery and Neurology, Holly Lane, Smethwick, Birmingham B67 7JX, UK

4 March 1988
Angioplasty and Thrombolysis in Surgery
Nottingham, UK
Information: Mr B R. Hopkinson FRCS, Consultant Surgeon, Queen's Medical Centre, University Hospital, Nottingham, UK

17–18 March 1988
Swiss Society for Thoracic and Cardiovascular Surgery 3rd Annual Meeting
Zurich, Switzerland
Information Assemblee Annuelle SSCTCV, c/o AKM Congress Service, PO Box CH-4005, Basel, Switzerland

13–15 April 1988
Annual Meeting of the Association of Surgeons of Great Britain and Ireland
Harrogate, UK
Information: Mr B. T. Jackson, The Royal College of Surgeons of England, 35/43 Lincoln's Inn Fields, London WC2A 3PN, UK

28–30 April 1988
20th Congress of the European Association for Gastroenterology and Endoscopy (EAGE)
Sirmione, Italy
Information Professor G. Bianchi-Porro (President EAGE), Ospedale 'L Sacco', Gastrointestinal Unit, 1-20157 Milan, Italy

17–28 April 1988
Advances in Neurosurgery
Glasgow/Edinburgh, Scotland, UK
Information Director, Courses Department, The British Council, 65 Davies Street, London W1Y 2AA, UK

21–23 April 1988
2nd Symposium for Surgery on the Fetus
Gmunden, Germany
Information Dr Wolfgang Metka, A-4020 Linz, Hauptplatz 29, Germany

28–30 April 1988
20th Congress of the European Association for Gastroenterology and Endoscopy (EAGE)
Sirmione, Italy
Information. Professor Dr med. J M. Kimmig, Vaihinger Strasse 43, D-7000 Stuttgart 80, FRG

5–7 May 1988
Biennial Congress of the European Council of Coloproctology 1988
Geneva, Switzerland
Information. General Secretary of the European Council of Coloproctology, Policlinique de Chirurgie, Hôpital Cantonal Universitaire de Genève, 1211 Geneva 4, Switzerland

8–11 May 1988
Joint Annual Meeting of the American Lung Association, the American Thoracic Society and the Congress of Lung Association Staff
Las Vegas, USA
Information Deborah Richardt, American Lung Association, 1740 Broadway, New York 10019, USA

12–14 May 1988
Second Vienna Shock Forum
Vienna, Austria
Information AUSTROPA Kongbressbüro, Friedrichstrasse 7, A-1010 Vienna, Austria

23–28 May 1988
Advanced Hepato-Pancreato-Biliary Surgery
Lund, Sweden
Information Professor Stig Bengmark, Box 5003, S-220 05, Lund 5, Sweden

25–28 May 1988
79th Annual Meeting of the American Association for Cancer Research
New Orleans, Louisiana, USA
Information. Margaret Foti, Executive Director, American Association for Cancer Research, Temple University School of Medicine, West Building Room 301, Philadelphia, PA 19140, USA

29 May–3 June 1988
Second World Congress on Hepato-Pancreato-Biliary Surgery
Amsterdam, The Netherlands
Information Q A. Laman Trip, Organizer, Alton House, Keizersgracht 792, 1017 EC Amsterdam, The Netherlands

5–11 June 1988
Tropical Medicine Update
Liverpool, UK
Information Director, Courses Department, The British Council, 65 Davies Street, London W1Y 2AA, UK

12–17 June 1988
Cardiovascular and Interventional Radiological Society of Europe
Berlin, FRG
Information Dr Reingard Sorensen, Klinikum Steglitz, Rontgendiagnostik, Hindenburgdamm 30, 1000 Berlin 45, FRG

20–22 June 1988
7th International Workshop for the Study of Vascular Anomalies
Hamburg, Germany
Information. Dr John B. Mulliken, The Children's Hospital, 300 Longwood Avenue, Boston MA 02115, USA

29 June–1 July 1988
International Symposium on Therapeutic Progress in Urological Cancers
Paris, France
Information: Dr Saad Khoury, clinique Urologique (Pr Chatelain), Hôpital de la Pitié-83, Boulevard de l'Hôpital, 75634 Paris Cedex 13, France

3–9 July 1988
16th World Congress of the International College of Surgeons
Milan, Italy
Information Secretariat, Clinica Chirurgica III—Università degli Studi, Via F Sforza 35, 20122 Milan, Italy

6–8 July 1988
The Third British Arthroscopy Symposium
Harrogate, UK
Information Mr M. R Phillips, Chas F Thackray Ltd., Shire Oak Street, Leeds LS6 2DP, UK

11–12 July 1988
Second Messenger Systems in Cellular Control—Prospects for New Drugs?
London, UK
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22–26 August 1988
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Information: Professor Stig Bengmark, Box 5003, S-220 05, Lund 5, Sweden

30 August–2 September 1988
10th World Congress Collegium Internationale Chirurgiae Digestive
Copenhagen, Denmark
Information. Secretariat, Spadille Congress Service, Sommervej 3, DK-3100 Hornbaek, Denmark

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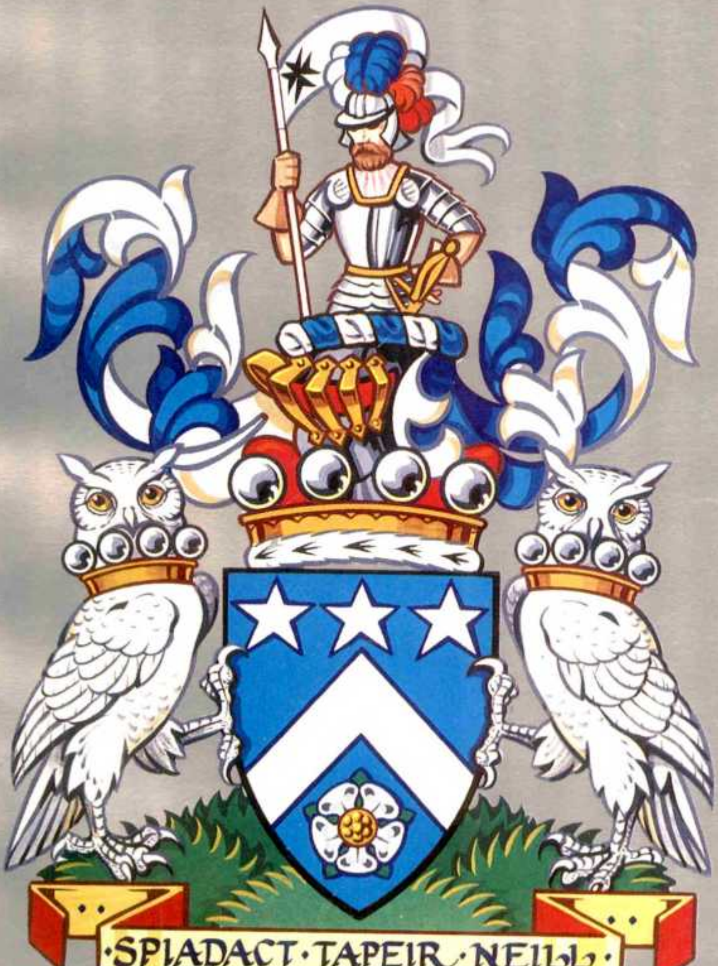
Volume 75, Number 3, March 1988

BJS 75



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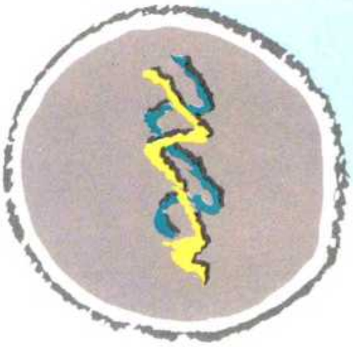

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Volume 75 Number 3 March 1988

LEADING ARTICLES

Choice of treatment in carcinoma of the oesophagus 193
T. P. J. Hennessy
Gastric varices: a proposed classification leading to management 195
S. W. Hosking and A. G. Johnson

REVIEW

Peroperative ultrasonography in the surgery of hepatic tumours 197
O. Traynor, D. Castaing and H. Bismuth

Clinical management of recurrent hepatocellular carcinoma after primary resection 203
T. Kanematsu, T. Matsumata, K. Takenaka, Y. Yoshida, H. Higashi and K. Sugimachi
Necrosectomy and postoperative local lavage in necrotizing pancreatitis 207
H. G. Beger, M. Büchler, R. Bittner, S. Block, T. Nevalainen and R. Roscher
Patient controlled analgesia and urinary retention (case report) 212
Nadia B. A. Hodsman, G. N. C. Kenny and C. S. McArdle
Biochemical prediction of gallstones in acute pancreatitis: a prospective study of three systems 213
B. R. Davidson, J. P. Neoptolemos, T. Leese and D. L. Carr-Locke
Surgical morbidity and mortality in one hundred and twenty-nine patients with obstructive jaundice 216
J. D. Greig, Z. H. Krukowski and N. A. Matheson
Pancreaticogastrostomy for pain relief in chronic pancreatitis 220
J. A. Pain and M. J. Knight
Contact laser or conventional cholecystectomy: a controlled trial 223
A. C. Steger, K. M. Moore and N. Hira

REVIEW

Blunt injuries of the diaphragm 226
C. D. Johnson

Management of penetrating abdominal stab wounds 231
A. M. de Lacy, M. Pera, J. C. Garcia-Valdecasas, L. Grande, J. Fuster, E. Cugat, M. A. Lopez-Boado, J. Visa and C. Pera
True radial artery aneurysm (case report) 233
W. H. Turner and A. R. Turnbull
Surgical approaches to vertebral artery injuries 234
C. Hatzitheofilou, D. Demetriades, J. Melissas, M. Stewart and J. Franklin
Doppler ultrasonography in the diagnosis of acute scrotal pain 238
K. I. Bickerstaff, K. Sethia and J. A. Murie
High prevalence of abdominal aortic aneurysm in men with peripheral vascular disease: screening by ultrasonography 240
J. T. Allardice, G. J. Allwright, J. M. C. Wafula and A. P. Wyatt
Ultrasound mammography in the management of breast cancer 243
D. J. Warwick, J. A. Smallwood, P. B. Guyer, K. C. Dewbury and I. Taylor
Relative merits of ultrasound and intravenous urography in the investigation of the urinary tract 246
B. Jagjivan, D. J. Moore and D. R. Naik
Intra-operative localization of bleeding small intestinal lesions 249
W. Y. Lau, S. Y. Wong, H. Ngan, S. T. Fan and K. K. Wong

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Venous mesenteric infarction: a particular entity
P.-A. Clavien, M. Dürig and F. Harder 252

Angiodysplasia of the colon: endoscopic diagnosis and treatment
J. C. M. Santos Jr, F. Aprilli, A. S. Guimarães and J. J. R. Rocha 256

Fate of the ischaemic limb in Buerger's disease
T. Ohta and S. Shionoya 259

Small bowel obstruction due to peritoneal encapsulation (case report)
S. P. J. Huddy and M. E. Bailey 262

Recurrent inguinal hernia: a personal study
A. J. Marsden 263

FOR DEBATE

Diagnosis of Meleney's synergistic gangrene
J. Davson, D. M. Jones and L. Turner 267

Gastric outlet loss and enterogastric reflux after gastrectomy
T. Ilci, P. F. Whitfield, P. B. Boulos and M. Hobsley 272

Treatment policy for the management of carcinoma of the oesophagus
L. Desa, A. S. Raghunath, S. L. Chawla, A. L. G. Peel and A. W. Dellipiani 275

Relationship between gastric emptying of liquid and postvagotomy diarrhoea
N. J. Parr, S. Grime, S. Brownless, M. Critchley, J. N. Baxter and C. R. Mackie 279

Bypass surgery for unresectable oesophageal cancer: early and late results in 124 cases
Aylwyn Mannell, P. L. Becker and M. Nissenbaum 283

Autotransplantation of lingual thyroid into the neck (case report)
A. Y. Izzidien Al-Samarrai, S. J. Crankson and A. Al-Jobori 287

Omental abscess: a rare complication after implantation of autologous splenic tissue into the omentum (case report)
M. Rhodes, T. W. J. Lennard and C. W. Venables 288

Colitis cystica profunda of the rectum treated by mucosal sleeve resection and colo-anal pullthrough (case report)
P. J. Guy and M. Hall 289

CORRESPONDENCE 290

BOOK REVIEWS 295

NOTICES AND ANNOUNCEMENTS 296

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Cover picture

Inception of the British Journal of Surgery

The idea that the United Kingdom should have its own English language surgical journal we owe to Professor Hey Groves of Bristol. Hey Groves was a distinguished surgeon, teacher and linguist and he had for some years organized a surgical journal club to review foreign journals. His attempts to persuade colleagues to join in publishing an English language journal had failed, at least up to 1912. Berkeley Moynihan of Leeds was known to Hey Groves as a dynamic provincial surgeon with an ability to 'get things done'. So when Moynihan was elected to the Council of the Royal College of Surgeons of England, Hey Groves decided to recruit him to lead the surgical journal.

Moynihan, truly the father of *The British Journal of Surgery*, had simultaneously been pondering a journal which would bring all the surgeons of England, Wales, Scotland and Ireland together but he too had received poor support for this idea from colleagues. Moynihan was not dissuaded and the meeting with Hey Groves convinced them both that a British surgical journal was possible. Hey Groves obtained the support of Mr Hartland Wright, the Bristol publisher, who undertook to finance and publish the new venture.

Moynihan considered the failure of previous attempts at a British journal was because they were 'too metropolitan', too parochial perhaps. Moynihan went first to the surgical knights, Sir Frederick Treves who had by then almost retired, Sir William McEwen and Sir John Bland-Sutton; at first they were discouraging. Moynihan's gift for personal manipulation carried the enterprise forward; a dinner party in London persuaded Bland-Sutton to join and McEwen was flattered into association by Moynihan's proposal to feature his clinic in the first number of the journal.

Moynihan used his drive and charm to recruit a large committee representative of London, the Provinces, the Scottish and the Irish schools; this ditched the 'metropolitan' negativeness. To expand the circulation, representatives of the Dominions and India were soon added to the committee by Hey Groves and Moynihan.

At the first committee meeting, held in the Examiners Room, Royal College of Surgeons of England on the 13 February 1913, Moynihan was elected Chairman, Hey Groves Editorial Secretary and Messrs Wrights were to be the publishers. Characteristics of today's *British Journal of Surgery* were settled at this initial meeting too: there would be a small Executive Committee, every paper would have two referees, the Journal would carry original articles, critical reviews and notes of rare cases (an ever popular section). Articles were to be illustrated with black and white figures, 'and in special cases by coloured drawings'. 'The net profits shall be divided in equal halves between the publishers and the Editorial Committee'.

At the second committee meeting on 10 April another milestone was achieved, 'The meeting was followed by dinner' at Pagini's restaurant.

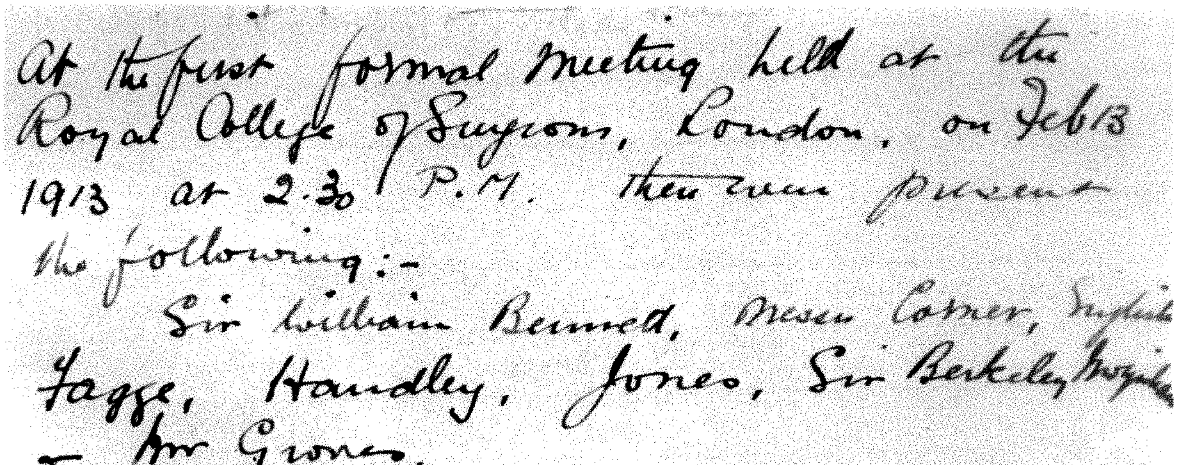
Moynihan remained Chairman of *The British Journal of Surgery* for the first 23 years, indeed he was Chairman when he died in 1936. In 1913 the first volume of the Journal had 748 pages and 7124 copies were sold. In 1936 there were 1024 pages and 9100 copies were sold. Moynihan set an amazing standard of chairmanship: up to 1934 he rarely missed a meeting and his signature to the minutes remained firm and legible to the end. His punctuality and geniality dominate the early minutes of the meetings.

Sir D'Arcy Power and Mr Gask had persuaded the Editorial Committee (at a meeting when Moynihan was not present on 9 May 1935) that a testimonial be presented to Lord Moynihan. This was agreed and on 6 July 1936 at the Royal College of Surgeons of England Moynihan was presented with a silver statuette from *The British Journal of Surgery*. On 9 July Moynihan presided over his last Annual Meeting of *The British Journal of Surgery*. He thanked the committee and offered to the Journal a replica of the statuette. This offer was received with acclamation.

At the next Editorial Committee Moynihan's death and *The British Journal of Surgery*'s loss were recorded.

Berkeley Moynihan

H. B. Devlin



At the first formal meeting held at the
Royal College of Surgeons, London, on Feb 13
1913 at 2.30 P.M. there were present
the following:-
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Fagge, Handley, Jones, Sir Berkeley Moynihan
& Mr Groves.

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Choice of treatment in carcinoma of the oesophagus

The prognosis for patients with carcinoma of the oesophagus has improved appreciably during the past decade. Not only has the mortality rate formerly associated with surgical resection fallen dramatically but improved 5-year survival rates are now regularly reported. Ellis and Maggs[1] resected 58 carcinomas with only 1 death and Akiyama *et al.*[2] achieved the remarkably low mortality rate of 1·4 per cent in over 200 resections. Orringer[3] reported a 6 per cent postoperative mortality rate for transhiatal resection. Skinner's[4] 5-year survival rate after *en bloc* resection of oesophageal tumours was 20 per cent, and 34·7 per cent of Akiyama's patients who underwent resection survived 5 years. The improved outlook for patients with oesophageal cancer undergoing surgery can be attributed to better pre- and postoperative care, particularly in the areas of nutritional and respiratory support. Developments in surgical technique such as *en bloc* resection and three-stage oesophagectomy have diminished the likelihood of anastomotic or local recurrence and has greatly reduced the risk of fatal anastomotic leakage.

Improvements in the results of radiotherapy have been less impressive. Evaluation of the role of radiotherapy is made difficult by the tendency to select patients with less advanced tumours (particularly those located in the lower third of the oesophagus) for resection leaving the more extensive and more proximal tumours for irradiation. Pearson's[6] results with a 25 per cent 5-year survival rate for patients with tumours of the cervical oesophagus, 16 per cent for those with mid-oesophageal tumours and 12 per cent for those with lower third carcinomas remain unchallenged in western countries. However, Huang and K'ai[7] have reported a 32·3 per cent 5-year survival rate for patients with tumours of the cervical oesophagus treated by radical radiotherapy. Controlled trials of radiotherapy *versus* surgery are virtually non-existent. The need for such trials is evident, particularly in the case of middle and upper third tumours.

The early results of combined treatment using chemotherapy, irradiation and resection have been encouraging[8] but it seems likely that any benefits in terms of tumour eradication may be offset by an increased mortality rate. However, the absence of viable tumour cells in resected specimens after chemotherapy and irradiation[9] suggests that it might be valuable to compare this form of combined therapy with resection alone.

Some element of preselection is inevitable in the referral pattern to specialized centres and for this reason the paper by Desa *et al.* (pp. 275–278) is an important contribution, outlining as it does the full dimension of the problem in a defined community over a 10-year period. It is clear that late presentation is the limiting factor in improving results. Effective palliation is, therefore, of the utmost importance. However, re-assessment of palliative procedures is indicated in the light of recent surgical and technological developments. Almost all published reports agree that resection of the tumour provides the best form of palliation. Surgical bypass offers an effective alternative. The operability rate in Desa's paper was disappointingly low, particularly in view of the excellent results of resection in the series, and it is reasonable to suggest that with the low mortality rates now attainable following surgery, more patients should be offered the benefits of palliative resection or bypass. Rigid adherence to strict criteria for operability is no longer justifiable. In a disease in which 50 per cent or more of the patients are aged between 60 and 70 years, age alone should not be a bar to surgery. Neither should the length of the tumour inhibit the decision to opt for surgery. Skinner[10] has pointed out that, provided the tumour has not breached the oesophageal wall, patients with tumours as long as 10 cm may become long-term survivors after resection. The value of CT scanning in identifying involvement of mediastinal structures is also questionable. Adequate cardiac and respiratory function and the absence of evidence of distant spread makes a patient a suitable candidate for palliative resection or bypass.

Radiotherapy is frequently chosen as a means of palliation but its effectiveness may be marred by serious complications. If the tumour is adherent to a bronchus a fistula

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may occur. Postirradiation stricture is not uncommon and dilatation of such strictures is dangerous. Up to 50 per cent of patients may have dysphagia after dilatation, limiting their diet to fluids and semi-solids.

Intubation should be reserved for patients with advanced disease and a very limited prognosis. Although pulsion methods of intubation are far superior to open traction methods and have a much lower mortality rate, intubation provides poor palliation. Blockage of the tube is not infrequent and swallowing is far from normal.

Laser therapy is much to be preferred as it preserves better oesophageal function with greater ease in swallowing and the treatment can be repeated. The relief of dysphagia provided by passage of an endoscope, or endoscopic dilatation, is very brief and the risk of perforation of the oesophagus in tight stenoses is not inconsiderable.

At present, resection seems to offer the best chance of long-term survival at least in the case of patients with tumours in the lower two-thirds of the oesophagus and also provides the best palliation with an acceptably low mortality rate. The establishment of controlled trials to compare surgery with the combination of irradiation and chemotherapy would appear to be the way forward.

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Gastric varices: a proposed classification leading to management

During the last decade there has been a renaissance of injection sclerotherapy for the treatment of oesophageal varices. As a result, considerable debate has arisen about the role of sclerotherapy in the pathogenesis and treatment of gastric varices. The problem is made worse by imprecise terminology and the limited and somewhat anecdotal literature on the subject.

Gastric varices usually arise because of generalized or segmental portal hypertension. The latter is most frequently caused by splenic vein thrombosis leading to the development of collateral venous channels and these pass via the short gastric veins and stomach wall to the portal vein through the left gastric vein. This generally results in varices of the gastric body and fundus, but not of the oesophagus. Should these varices bleed, treatment consists of splenectomy and direct ligation of the bleeding varix[1]. In contrast, gastric varices arising in patients with generalized portal hypertension are accompanied, almost invariably, by oesophageal varices and are often grouped with them and termed gastro-oesophageal varices[2]. This is misleading, as it implies that gastric varices behave like, and can be treated in the same way as, oesophageal varices.

Unlike oesophageal varices, the prevalence of gastric varices is unknown but it seems they are uncommon. Madsen's review of the world literature on gastric varices following splenic vein occlusion found 207 patients[1]. Major sclerotherapy trials in patients with oesophageal varices and generalized portal hypertension barely mention gastric varices, and other large series refer only to 'gastro-oesophageal varices'. Our own experience during the last 7 years is that, of 208 patients treated for bleeding from either gastric or oesophageal varices, 14 (6 per cent) were noted to have gastric varices at the initial endoscopy and in 5 they were the source of bleeding; a further 21 patients developed gastric varices during long-term follow-up. Recognizing gastric varices endoscopically can be difficult as they lie in the gastric submucosa[3] and may be obscured by rugae. Sometimes barium studies reveal fundal varices but the appearances may be confused with tumour; endoscopy in these situations often fails to show either tumour or varices[4]. This has led others to rely on splenoportography as a diagnostic technique[1]. For patients in whom gastric varices are suspected, splenoportography often demonstrates large vessels in the region of the stomach, but it cannot determine the relationship of the vessels to the gastric mucosa. For example, splenoportography revealed dilated veins around the stomach in 11 of one series of 12 cirrhotic patients, the majority of whom had no evidence of fundal or oesophageal varices on barium studies[5]. In another series of 57 patients undergoing splenoportography as part of their evaluation for shunt surgery (49 having previously bled from 'varices'), 31 patients had angiographic evidence of moderate to large gastric varices[6]. One group performed both endoscopy and splenoportography and of 10 patients diagnosed as having gastric varices on splenoportography, only 4 had this confirmed endoscopically[4]. These findings highlight a very important point: that large collaterals develop in the majority of patients with portal hypertension, but they are of clinical importance only when they are close enough to the gut lumen to rupture. Splenoportograpy cannot give this information. It might be asked whether sclerotherapy of oesophageal varices causes, or exacerbates, gastric varices. This is unlikely in view of the many extramucosal collaterals around the gastric fundus and, in our experience, there was no correlation between the appearance of gastric varices and the timing or completeness of obliteration of oesophageal varices during long-term sclerotherapy.

What then is a gastric varix? Certainly, any varix seen within the stomach by an endoscope should be so named, but this is not common. On the other hand, we have seen a venous jet emerging from an apparently normal stomach wall, indicating an invisible underlying gastric varix. Despite these problems, it is important to search carefully for and document gastric varices, for several reasons: first, a proportion eventually bleed (60 per cent in our experience); second, until 10 years ago, differentiating between gastric or oesophageal varices as the source of bleeding was not important, as both would usually have been treated by a porta-systemic shunt. Now that this has become less popular with the widespread use of injection schlerotherapy, differentiation becomes important again; injection sclerotherapy has proved far less useful for treating gastric varices[7,8].

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There are exceptions. Gastric varices which are a continuation of oesophageal varices extending below the squamocolumnar junction into the stomach respond well to sclerotherapy, in our experience. In some of these, the blood flow is from oesophagus to stomach, as shown by Doppler studies[9], which would make sclerotherapy effective; but even in those with cephalad flow, a thrombus at the junction can propagate against the flow. Nineteen of our patients have bled from such gastric varices and sclerotherapy achieved long-term control in all but three. This is in contrast with the disappointing results of sclerotherapy to fundal varices where serious complications and deaths due to the procedure exceed 25 per cent[7,8]. Because of these differences we suggest that gastric varices should be documented in a way that is relevant to management and which avoids confusion in terminology. We propose the following classification:

Type 1 varices are those which appear as an inferior extension of oesophageal varices across the squamocolumnar junction—these can be treated by injection sclerotherapy;
Type 2 are gastric varices (nearly always accompanied by oesophageal varices) located in the fundus, which appear to converge towards the cardia—these can be treated by devascularization or shunting if they bleed;
Type 3 are gastric varices located in the fundus or body in the absence of oesophageal varices and which appear unconnected to the cardia—these can usually be treated by splenectomy.

In our experience, type 1 gastric varices appeared in 20 of 208 patients receiving sclerotherapy at varied times from 1 week to 3 years after injecting oesophageal varices. In four patients they were present before any sclerotherapy had been given. All were treated by intravariceal injection of sclerosant at the squamocolumnar junction, with the result that bleeding was controlled and/or the varices disappeared.

Type 2 varices are less common and were seen in only four of our patients at their presentation with bleeding oesophageal varices. After sclerotherapy of the oesophageal varices, gastric varices disappeared in two patients but appeared without bleeding in another. In view of the poor results obtained from injecting fundal varices with sclerosant[7] we advocate variceal ligation and gastric devascularization for bleeding type 2 gastric varices. Others may prefer some form of shunt procedure. If type 1 and 2 gastric varices coexist and bleed, we treat them according to type.

Type 3 gastric varices usually result from segmental portal hypertension; because they are often difficult to visualize, the cause of bleeding may remain obscure in 50 per cent of patients at the time of their first bleed[1]. When endoscopy fails to reveal varices, a normal liver biopsy and portal pressure, combined with angiographic evidence of gastric varices, suggests the diagnosis. Splenectomy and direct varices ligation is curative.

There is no evidence so far to justify prophylactic treatment of non-bleeding gastric varices.

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Peroperative ultrasonography in the surgery of hepatic tumours

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This article reviews the value of peroperative ultrasonography in the detection, localization and management of liver tumours.

Keywords: Intra-operative ultrasonography, hepatic surgery

Ultrasonography is a non-invasive method of exploring the liver, and has been responsible for major advances in diagnosis in hepatobiliary surgery over the last 15 years. However, the usefulness of ultrasonography has always been limited by two factors: ultrasound travels poorly in air, and adjacent pulmonary and bowel gas frequently interfere with image-quality; and the subcostal location of the liver renders it inaccessible to complete exploration by an ultrasound probe.

For these reasons, ultrasound examination of the liver necessitates using ultrasound of quite low frequency (3·5 MHz) and this often results in poor resolution. Nevertheless, in recent years, ultrasonography combined with other methods of morphological exploration (CT scanning and arteriography) has allowed fuller assessment of the liver pre-operatively. These pre-operative assessments have meant that laparotomy undertaken to make a diagnosis is a thing of the past but the surgeon is still frequently faced with the following questions in the operating room: What exactly is the nature of the lesion in this liver? Where exactly is it situated? How can it best be approached without damaging the vascular structures and parenchyma in the rest of the liver?

Largely as a result of the need to answer these questions, the idea of applying an ultrasound probe directly to the liver during surgery has gradually evolved.

The first reports of peroperative ultrasonography were made more than 20 years ago by Knight and Newell[1] and by Eiseman *et al.*[2]. They used A-mode scanners and difficulties in interpretation of the images limited advancement of the technique. The development of real time B-mode scanners has resulted in images which are easier to interpret. Furthermore, by applying an ultrasound probe directly to the surface of the liver the obstacles posed by the abdominal wall, the rib cage and adjacent pulmonary and bowel gas are overcome (*Figure 1*). It is possible, therefore, to use higher frequency sound, with better resolution and better image-quality. The use of peroperative ultrasonography using these real time B-mode scanners has been largely advanced by Japanese authors who have used this technique to increase surgical possibilities and to develop new surgical procedures which are specifically adapted to individual lesions[3–5].

Peroperative ultrasonography is now firmly established in the armamentarium of the liver surgeon and certain recently described techniques are quite impossible without it. In this report we describe the technical aspects, methodology, and applications of peroperative ultrasonography in liver surgery with illustrations drawn from the experience of this unit over the past 4 years in 672 patients undergoing abdominal surgery (*Table 1*).

Technical considerations

The equipment used for peroperative ultrasonography is an ordinary real time, linear array, B-mode scanner which is not specifically designed for peroperative use. We use the Scanel 300

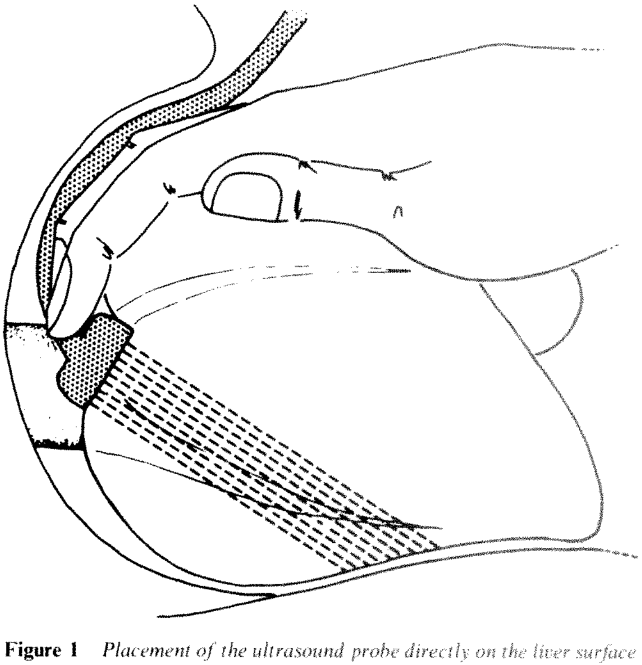

Figure 1 *Placement of the ultrasound probe directly on the liver surface avoids bowel gas and the rib cage, and allows the use of high frequencies resulting in better image quality*

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Table 1 *Patients studied by peroperative ultrasonography between June 1982 and June 1986*

Nature of lesion	Number of patients	In comparison with pre-operative studies: Supplementary information	In comparison with pre-operative studies: Change in surgical tactics
Liver tumours			
Hepatocellular carcinoma	71	24	19
Liver metastases	123	44	19
Benign tumours	23	7	2
Other tumours	210	33	7
Portal hypertension	49	10	2
Biliary surgery	119	22	6
Miscellaneous	77	15	1
Total	672	155	56

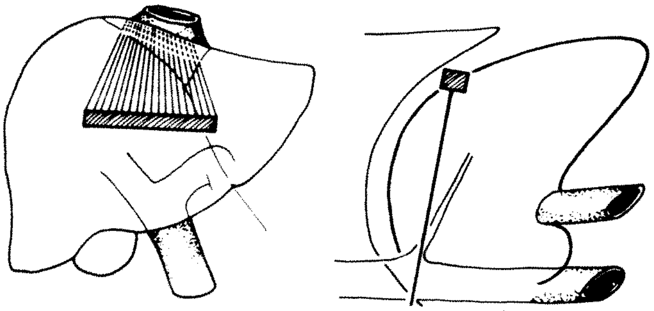

Figure 2 *Peroperative ultrasound examination begins by placing the probe on the anterior surface of the liver facing towards the junction of the hepatic veins with the inferior vena cava*

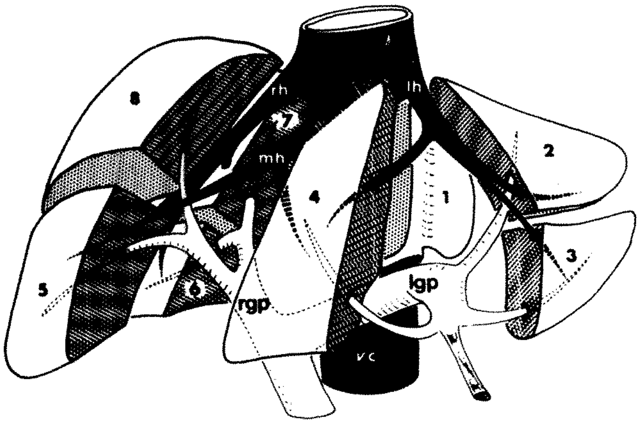

Figure 3 *Segmental anatomy of the liver (after Couinaud): rh, right hepatic vein; mh, middle hepatic vein; lh, left hepatic vein; rgp, right Glissonian pedicle (portal vein, hepatic artery, bile duct); lgp, left Glissonian pedicle; vc, inferior vena cava; 1–8, liver segments*

and Scanel 500 machines (CGR Ultrasonic, 77400 Meaux, France) but other commercially available machines can be used. The only part of the equipment which is purpose-built is a linear probe of 7 × 2 × 0·8 cm the structure of which is specifically designed for exploration of the liver beneath the diaphragm. It uses a frequency of 5 MHz and is watertight and can be sterilized. The linear probe has the dual advantages of small size and allowing ready recognition of anatomical structures. The conventional sectorial probe distorts the images it receives and this complicates anatomical recognition and makes target biopsy more difficult.

At the start of each examination the apparatus is placed close to the operating table, and the sterile connecting cable is passed out to the machine operator. The sterile probe is then placed directly on the liver surface by the surgeon who will perform the examination. In general, the natural humidity of the liver is sufficient to ensure a good ultrasound contact without the need for a contact gel. The apparatus is operated by a technician, nurse, or medical student according to the instructions of the surgeon, but the assistance of a radiologist may be very valuable. The images appear on a monitor on the ultrasound machine and they can be frozen and recorded photographically if desired. The operator, manipulating the probe under direct vision, can easily correlate the images obtained from within the liver with the external anatomical landmarks.

Methodology and anatomical landmarks

The aims of a peroperative ultrasound examination are: to define anatomical landmarks and anatomical boundaries within the liver; to identify abnormal areas in the hepatic parenchyma; and to establish the relationship of any abnormal areas with the intrahepatic vascular structures and thus to localize them precisely. A complete examination therefore consists of identifying the vascular landmarks, then delineating the various segments as described by Couinaud[6], and finally assessing the hepatic parenchyma in each segment. The order of examination is not of great importance but it is essential to have a system which is always followed to avoid errors and omissions. A complete peroperative ultrasound examination can be performed in 5–10 min.

It is convenient to commence the examination by identifying the confluence of the three hepatic veins with the inferior vena cava. To do this, the probe is placed obliquely upwards (*Figure 2*). The hepatic veins can often be recognized by transmitted heartbeats and by the presence of moving acoustic shadows within them. By recognizing the position and course of the three hepatic veins the four sectors of the liver can immediately be defined (*Figure 3*): right lateral sector, posterior to the right hepatic vein containing segments VI and VII; right paramedian sector, between the right hepatic vein and the middle hepatic vein, and containing segments V and VIII; left paramedian sector, between the middle hepatic vein and the left hepatic vein and containing segments IV and III; and left lateral sector, posterolateral to the left hepatic vein, and containing segment II.

To further divide these sectors into the individual segments it is necessary to define the portal pedicles to each segment. This is achieved by first identifying the hilar region and the portal bifurcation. To do this the probe is placed a little further down on the anterior surface of the liver, facing directly towards the hilum.

The portal pedicles are surrounded by a prolongation of Glisson's capsule, giving them a characteristic ultrasonographic appearance which makes identification easy even in the periphery of the liver. All three elements of the portal pedicles (portal vein, hepatic artery and bile duct) are usually visible only in the hilar region. The portal vein, however, can be followed out to the left at the recess of Rex, the individual branches to

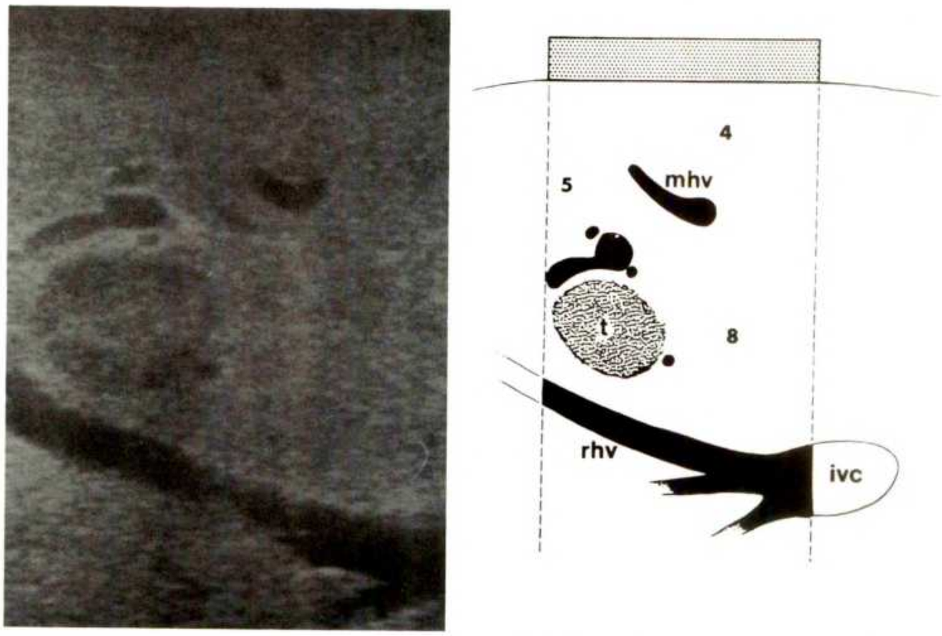

Figure 4 *1 cm tumour deeply placed in the right half of the liver between the right hepatic vein (rhv) and middle hepatic vein (mhv) and close to the posterior branch of the anterior trunk of the right portal vein (i.e. in segment VIII); ivc, inferior vena cava*

segments II, III and IV being identified. Similarly it can be followed to the right, identifying (a) the anterior division of the right portal branch which in turn divides to supply segments V anterior) and VIII (posterior), and (b) the posterior division of the right portal branch which in turn divides to supply segments VI (anterior) and VII (posterior).

The definition of the segmental anatomy is now complete except for segment I, the caudate lobe, which lies between the portal bifurcation and the inferior vena cava, its left extremity being delineated by the insertion of the lesser omentum. Having defined the eight liver segments (*Figure 3*) the parenchyma of each segment is then examined systematically and the relationship of any abnormal area to the vascular structures is established.

Ultrasonography can detect areas of altered texture (i.e. homogeneous or heterogeneous parenchyma), areas of altered echogenicity (hyperechogenic, hypo-echogenic or anechogenic lesions) and acoustic shadows. The final stage in the examination consists of assessing the gallbladder and the hepatic pedicle. It is important to remember that the intrahepatic vascular anatomy is not always constant and some of the more commonly encountered anomalies have previously been described in detail[7,8].

General applications

Tumour recognition

Tumour recognition is the first and most important practical application of peroperative ultrasonography. When a tumour has been identified pre-operatively (by ultrasonography or CT scan) it is usually quite easy to find it peroperatively by inspection and palpation. However, tumour recognition at the time of operation can be difficult or impossible: if pre-operative tests have not demonstrated a definite tumour and there is simply a high index of suspicion (e.g. elevated α-fetoprotein levels in a cirrhotic patient); if the hepatic parenchyma is abnormally hard (e.g. in cirrhosis or severe cholestasis); of if there is a very small, deeply placed tumour. In these situations peroperative ultrasonography may be indispensable for tumour recognition (*Figure 4*). When a tumour has been identified in the liver, the recognition of daughter nodules or metastatic deposits is also crucially important, as this may have important implications regarding the indications for surgical resection.

We prospectively examined pre- and peroperative assessment of the liver in 98 patients undergoing abdominal surgery[9]. A total of 25 patients had hepatocellular carcinoma, 25 had liver metastases, 6 had benign tumours and 42 had digestive tract cancers without liver metastases. Some of the patients with tumours had more than one tumour in the liver. All 98 patients had pre-operative ultrasonography, 45 had a CT scan and 50 had hepatic arteriography. Peroperative ultrasonography was more sensitive than any of the pre-operative examinations, particularly in the detection of tumours <1 cm in diameter. In 13 of 40 tumours <1 cm diameter (32 per cent) were detected only by peroperative ultrasonography and were not even detectable by very thorough palpation of the liver at laparotomy; 1 of the 60 tumours >3 cm diameter was detected only by peroperative ultrasonograpy.

Tumour identification

The precise identification of the nature of a tumour (benign or malignant, primary or secondary) is not always possible pre-operatively despite a full range of assessments (biochemical tests, ultrasonography, scintigraphy, CT scanning and angiography). However by identifying an abnormal area in the liver during surgery, the ultrasound probe can be placed directly over the area and a precisely directed target biopsy can be performed, at the same time avoiding any major vascular structures.

Tumour localization

Modern hepatic resection is based on the internal anatomy of the liver as described by Couinaud[6,10]. The eight segments (*Figure 3*) each have a completely independent arterial, portal venous, and hepatic venous vascularization. It is therefore possible to electively excise one of these segments without damaging the blood supply to the others.

In order to do this it is essential to define the borders between the different segments (i.e. to define the vascular pedicles). The surface of the liver however gives no clue to the position of the internal vascular structures and so limited hepatic resections (i.e. segmentectomies) are almost impossible without peroperative ultrasonography. By placing the ultrasound probe directly over the various vascular structures their position and course can be traced on the liver capsule with diathermy and the segment to be excised can be 'mapped-out'

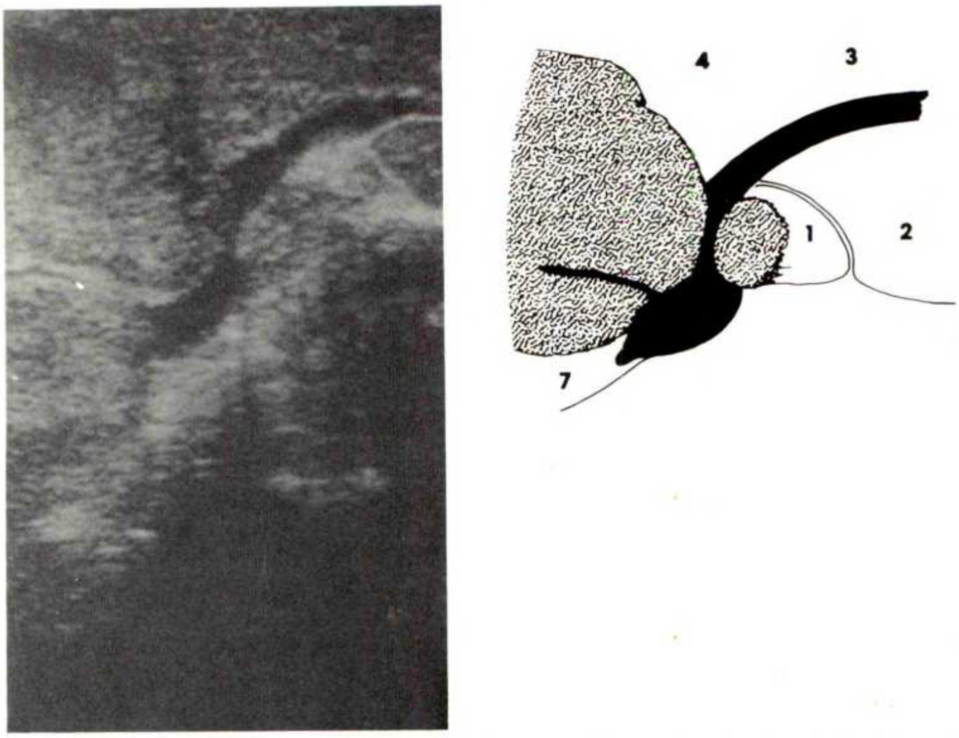

Figure 5 *Placement of the probe on the anterior surface of the liver reveals tumour involving the middle hepatic vein and both sides of the left hepatic vein (i.e. inoperable)*

on the liver surface before resection begins[7–9]. By localizing the tumour precisely and by planning the resection carefully in advance the surgeon will always know exactly what margin of healthy tissue will be excised around the tumour.

Modification of surgical tactics

At the start of any laparotomy an ultrasound probe can be passed through a small preliminary incision to examine the liver and determine if there are any formal contra-indications to continuing the operation (*Figure 5*). A more complete ultrasound assessment, with biopsies if necessary, can be performed when the abdomen has been fully opened and the liver has been mobilized. At a later stage, during liver resection, the ultrasound probe can be repeatedly used to control the direction of section and the depth of excision required.

Special applications

Surgery for hepatocellular carcinoma in cirrhosis

Peroperative ultrasonography is virtually indispensable in the resection of hepatocellular carcinomas in the cirrhotic liver, as modifications in the hepatic parenchyma often make identification of the tumour by palpation almost impossible[5,11]. Furthermore there are frequently areas of segmental atrophy and hypertrophy in the cirrhotic liver which make appreciation of the segmental borders very difficult by simple inspection or palpation.

Peroperative ultrasonography is not only of value in the detection and localization of tumours in the cirrhotic liver but is also an important aid in planning their excision. The principal mode of dissemination of hepatocellular carcinoma is by the portal venous route[12]. As the tumour increases in volume it eventually breaches the wall of the portal vein and tumour thrombus may then develop in the portal vein lumen. This tumour thrombus grows against the current toward the main portal trunk. However, at each portal bifurcation friable fragments may break off and be carried distally by the portal venous flow where they grow and form daughter nodules of the primary tumour (*Figure 6*). An oncologically acceptable resection for hepatocellular carcinoma therefore should include not only the primary tumour with an adequate margin of healthy tissue at its periphery, but also all hepatic parenchyma susceptible to daughter nodule development from portal vein thrombi. To do this it is essential to know the proximal extent of portal vein spread and peroperative ultrasonography can be very helpful in this regard (*Figure 7*). This is particularly important in the cirrhotic patient where the balance between oncological acceptability and postoperative liver insufficiency is very delicate[13].

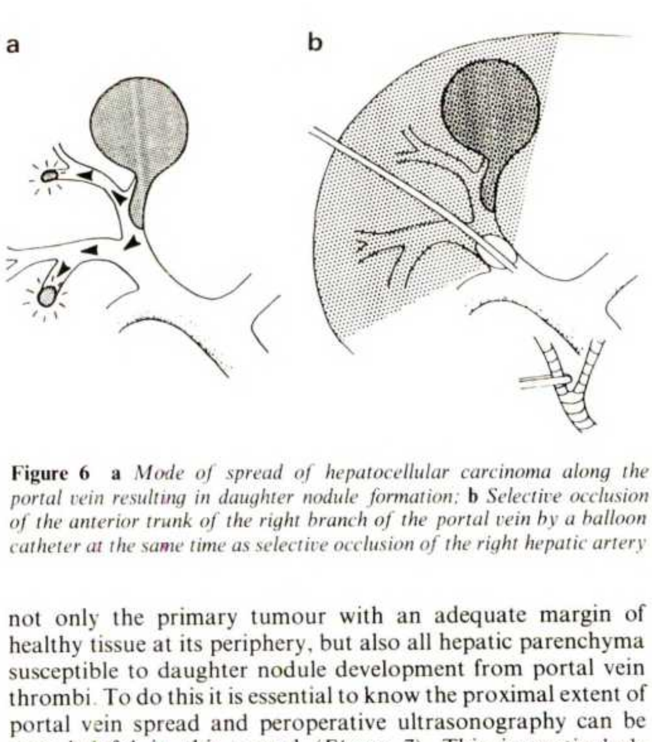

Figure 6 **a** *Mode of spread of hepatocellular carcinoma along the portal vein resulting in daughter nodule formation;* **b** *Selective occlusion of the anterior trunk of the right branch of the portal vein by a balloon catheter at the same time as selective occlusion of the right hepatic artery*

Finally peroperative ultrasonography can aid the resection itself in cirrhotic patients. Under ultrasound guidance the portal vein branch supplying the segment to be resected can be punctured and a dye (e.g. methylene blue) can be injected[12]. Within a few minutes this dye will stain all of the parenchyma supplied by the portal branch, thus clearly marking the limits of the resection. Alternatively, a balloon catheter can be inserted into the portal branch supplying the segment to be resected (*Figure 6b*). The balloon is then inflated, thus arresting portal venous flow to that segment. By clamping the appropriate

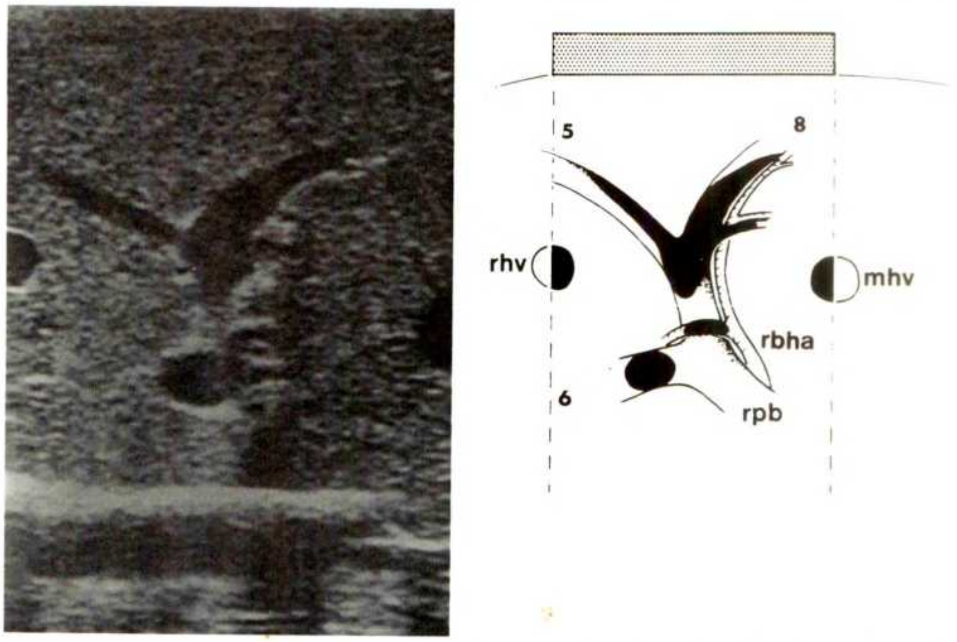

Figure 7 *Tumour in the anterior trunk of the right portal vein (branches to both segments V and VIII). There is also tumour thrombus in the posterior trunk (segment VI): rpb, right portal vein; rbha, right branch of hepatic artery; rhv, right hepatic vein; mhv, middle hepatic vein*

branch of the hepatic artery at the hilum of the liver a total vascular exclusion of one segment is obtained while maintaining blood supply (or at least portal venous supply) to the rest of the liver[12]. The segmentectomy can then be performed under relatively avascular conditions.

Recent reports from Japanese[12,14] and Chinese[15] centres have shown that these limited liver resections for small hepatocellular carcinomas in cirrhosis are compatible with 3-year survival rates of >50 per cent. This certainty should encourage systematic screening in cirrhotic patients at high risk of developing hepatocellular carcinoma. Among the 71 hepatocellular carcinomas which we have studied by peroperative ultrasonography, 60 were in cirrhotic patients (85 per cent). In 24 instances (34 per cent) the peroperative ultrasonography gave additional information either by the discovery of daughter nodules or by providing additional topographical details. As a result, in 19 cases (27 per cent) the surgical tactics were changed; in 7 cases a contra-indication to resection was discovered, in 10 cases a more limited resection than planned was shown to be possible, and in 2 cases a larger resection was required.

Surgery for liver metastases

Limited liver resections (segmentectomies) can be performed for liver metastases in the same manner as just described for primary liver tumours. These limited resections do not carry the same risks as major liver resections and they leave open the option of repeated resection in the event of tumour recurrence. On the other hand they confer a better prognosis than simple metastasectomies[16,17]. Fundamental to the decision to proceed with a limited resection in the presence of liver metastases is a precise knowledge of the site, size and extent of tumour. This can best be demonstrated by peroperative ultrasonography.

In the 123 patients with liver metastases who we studied, the peroperative ultrasound examination supplemented the information provided by the pre-operative tests in 44 cases (36 per cent) and the surgical tactics were changed as a result in 19 cases (15 per cent). In five instances the decision to resect was abandoned, in eleven cases a more limited resection was permitted, and in three instances a more extensive resection was required.

Surgery for benign liver tumours

By aiding precise target biopsy of all liver lesions, peroperative ultrasonography permits a definitive histological diagnosis to be made before making a decision to resect. In this way the surgical procedure, if warranted at all, can be better adapted to the nature of the lesion and extensive 'blind' resections can be avoided.

Discussion

In conclusion, peroperative ultrasonography responds well to the needs of the surgeon when undertaking possible resection of a liver tumour. In many ways the ultrasound probe can be considered as an extension of the surgeon's hand and eye, allowing him to 'see' inside an organ whose volume and character have traditionally made surgical exploration difficult, and allowing the discovery of tiny tumours at a time when limited resections may offer real hope of increased survival. Fifty years ago the practice of biliary surgery was dramatically transformed through the introduction of peroperative cholangiography. In the same way the practice of hepatic surgery, particularly in relation to the resection of liver tumours, is currently undergoing a dramatic transformation through the introduction of peroperative ultrasonography.

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Clinical management of recurrent hepatocellular carcinoma after primary resection

Curative resections were performed on 121 patients with primary hepatocellular carcinoma from 1975 to 1986 at Kyushu University Hospital, Japan. Up to August 1987 there was a recurrence in 41, detected between 4 and 86 (mean 20) months after surgery. Intrahepatic recurrences were the most common (82 per cent). There was no statistically significant correlation between size of the primary tumour and interval from surgery to detection of recurrence (r = −0·09). Serial measurement of serum α-fetoprotein (AFP) was useful for the detection of recurrences. However, the levels of AFP seem to be a non-specific, unreliable test for such patients since this tumour marker showed different ranges before the primary surgery and at the time of recurrence in 5 of the 41 patients (12 per cent). Postoperative chemotherapy with oral 5-fluorouracil had no apparent preventative effect on the recurrence. A second curative resection was effective in four patients, and three survived for over 2 years; the longest survival time is 9 years after the second procedure.

Keywords: Hepatocellular carcinoma, liver resection, recurrence

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Hepatocellular carcinoma (HCC) is one of the most malignant of solid tumours, in terms of prognosis[1], and is the third major cause of cancer death in males and the fifth among females in Japan[2]. The condition is increasing in the Western countries[3,4].

Diagnosis of HCC at an early stage has been greatly enhanced by the advent of screening techniques such as serum α-fetoprotein (AFP) measurement and ultrasound examinations[5]. In patients with early HCC, liver resections are easier and the prognosis of surgically treated patients is significantly better than that of patients treated medically, both in the Eastern and Western countries[6–8]. In 1984 we reported that 1-, 2- and 5-year survival rates of cirrhotic patients with limited hepatic resection were 79·9, 60·3 and 32·6 per cent, respectively[9]. Similar rates were reported in the USA[10]. While the results of surgical treatment of HCC are encouraging[11,12], the long-term survival rate after curative resection remains low because of the high rate of recurrence. Lee *et al.*[13] reported that the 1-year mortality rate due to recurrence after surgery was 24 per cent in patients with symptomatic HCC and 8 per cent in the asymptomatic group.

We followed our patients closely to detect recurrence and to determine the effect of chemotherapy on survival and the feasibility of further resection.

Patients and methods

Patients

From 1 January 1975 to 31 December 1986, 570 Japanese patients with HCC were admitted to the Department of Surgery II, Kyushu University Hospital. Of these 570 patients, 121 underwent curative hepatic resection: 3 extended right lobectomies, 17 right lobectomies, 5 left lobectomies, 16 subsegmental resections and 80 partial hepatectomies. Twenty-eight died within the first six postoperative months, including 14 deaths within 30 days. Liver failure was responsible for death in 20 of the 28 patients. Intra-abdominal infection was also a contributing factor in six patients. Extensive sepsis led to death in one patient, as did bleeding duodenal ulcer in another patient. The choice of adjuvant chemotherapy was based on the clinical status of the patient and the results of postoperative liver function tests. Among the 93 who survived for over 6 months, 20 were prescribed daily oral 5-fluorouracil (5-FU) 600–800 mg, for as long as was tolerated. No adjuvant chemotherapy was given to the remaining 73 patients. We traced every patient up to 1 August 1987.

The term 'curative' used in the present study means the removal of all gross tumours. Regarding recurrence, it was difficult to distinguish deaths due to non-excised cancer tissues, unrecognized multifocal primary tumours and new primary tumours. In the present study, all the tumours that developed following a curative resection were included as a recurrence.

Follow-up study

After hepatic resection, patients were seen regularly every 1 or 2 months during the first three postoperative years, and at 6-month intervals from years 4 to 10. Follow-up comprised a clinical examination and blood chemistry. Serum AFP concentrations were measured by radioimmunoassay at least twice before the primary surgery, at the first visit to the clinic and just before the operation. The levels of serum AFP were measured postoperatively when the patient visited the clinic. From 1975 to 1978, liver scans using ^{99m}technetium sulphur colloid were performed. After ultrasound and computed tomography (CT) became available in 1979, combinations of ultrasound, CT and liver scans together with chest X-ray were performed at 6-month intervals The scans were evaluated by radiologists. When recurrence was suspected, patients were re-admitted and angiographic evaluation was made.

Treatment

When the recurrence was local and resectable, and clinical status and liver function of the patients were deemed adequate, hepatic re-resection was done. After detection of a non-resectable recurrence of the liver cancer, adjuvant chemotherapy was given according to the clinical status of each patient. Between 1975 and 1981, these patients were prescribed oral 5-FU. Selective targeting cancer chemotherapy, using an oily contrast medium (Lipiodol), was introduced in 1982 in our department[14]. Lipiodolization involves the administration of chemotherapeutic agents suspended in Lipiodol and given through feeder arteries, using the Seldinger technique[15], the objective being selective cancer chemotherapy. Doxorubicin (Adriamycin) 15–80 mg/mm² was mixed in 4–8 ml of Lipiodol and given through feeder arteries. As a rule, this treatment was repeated about every 6 months and was given when the recurrence was apparently confined in the liver. When the patients had a disseminated tumour in distant organs, systemic chemotherapy was prescribed.

Statistical analyses

The correlation of tumour size and intervals between surgery and detection of recurrences was determined, using the least-squares linear regression analysis. Survival rates were analysed by the method of Kaplan and Meier[16]. The significance of difference in rate of recurrence

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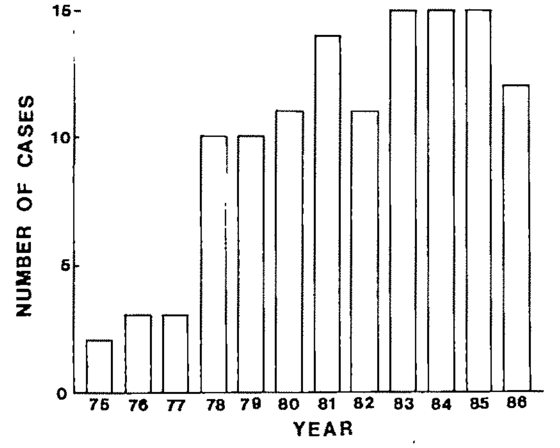

Figure 1 *Yearly distribution of 121 curative hepatic resections for hepatocellular carcinoma performed from 1975 to 1986 in our institute*

Table 1 *Intervals from primary surgery to diagnosis of recurrence of hepatocellular carcinoma*

Months postoperatively	No. of patients ($n = 41$)
0–12	19 (46)
13–24	7 (17)
25–36	9 (22)
37–48	2 (5)
49–60	2 (5)
>60	2 (5)

Values in parentheses are percentages

of patients with or without adjuvant chemotherapy was compared using the Fisher exact test.

Results

Incidence

The yearly distribution of curative hepatic resections for HCC performed from 1975 to 1986 is shown in *Figure 1*. All the liver tumours were histologically verified HCC, and the fibrolamellar variant was evident in one patient. Of the 121 patients, 93 survived for over 6 months, and by August 1987 there were 41 recurrences. Of these, 33 were men and 8 women with an average age of 57·7 (range 36–75) years at the time of detection of recurrence. Thirty-three (80 per cent) had a histologically proven cirrhosis, four (10 per cent) hepatic fibrosis and one (2 per cent) chronic active hepatitis. There was no evidence of concomitant liver disease in three individuals (8 per cent). Hepatitis B surface antigen was positive in the sera of seven patients (17 per cent).

Interval from primary surgery to diagnosis of recurrence

Recurrences were detected between 4 and 86 (mean 20) months after radical removal of primary tumours in 41 patients (*Table 1*). One patient who underwent curative resection for a second tumour had a third tumour 59 and 34 months after first and second radical resections, respectively.

There was no significant correlation between size of the primary tumour and interval from the primary surgery to the detection of recurrence (*Figure 2*) ($r = -0{\cdot}09$).

Recurrences were confined to the liver in 33 patients (82 per cent) and to the lungs in 3 patients (8 per cent) (*Table 2*).

Recurrence was suspected in 14 patients (34 per cent) on the basis of elevated serum AFP, and ultrasound examination demonstrated recurrent masses in the livers of 7 patients (17 per cent) (*Table 3*).

For convenience, ranges of AFP values were divided into the following four categories: normal (<20 ng/ml), low (20–100 ng/ml), moderate (100–1000 ng/ml), high (>1000 ng/ml). *Table 4* shows the relationship between serum AFP values before removal of the primary tumour and after detection of recurrence.

Effect of postoperative adjuvant chemotherapy with 5-FU

There was no statistically significant difference in the rate of recurrence between the group who had chemotherapy and those who did not (*Table 5*).

Outcome

The Kaplan–Meier life table estimate of the cumulative survival for 107 patients, excluding 14 operative deaths, showed

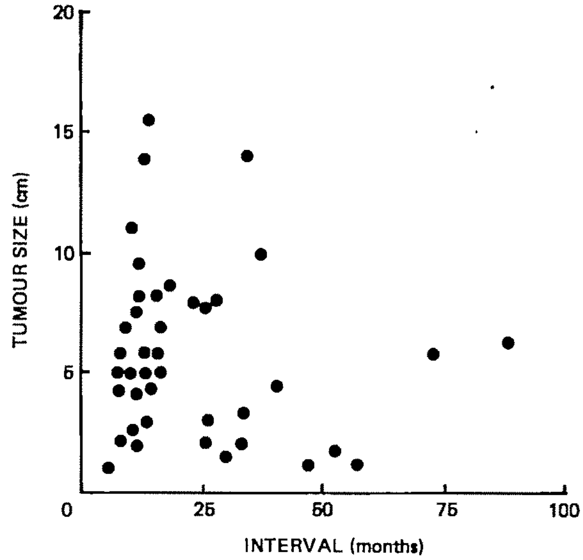

Figure 2 *Relationship between size of primary tumour and interval from primary surgery to detection of recurrence. There was no statistical correlation* ($r = -0{\cdot}09$)

Table 2 *Sites of recurrences of hepatocellular carcinoma at time of detection*

Sites	No. of patients ($n = 41$)
Liver only	33 (82)
Lung only	3 (8)
Liver–lung	1 (2)
Liver–brain	1 (2)
Lung–skin	1 (2)
Skin	1 (2)
Regional lymph nodes	1 (2)

Values in parentheses are percentages

Table 3 *Investigations used to detect recurrence of hepatocellular carcinoma*

Investigations	No. of patients ($n = 41$)
α-Fetoprotein	14 (34)
Ultrasound	7 (17)
Liver scanning	3 (7)
Chest X-ray	2 (5)
Computed tomography	1 (2)
Abnormal liver chemistry	1 (2)
Combination of hepatic imagings	
Two modalities	3 (7)
Three modalities	5 (13)
Others	5 (12)

Values in parentheses are percentages

Table 4 *Serum AFP values before primary surgery and after detection of recurrence of hepatocellular carcinoma*

AFP values before primary surgery	No. of patients	AFP values after detection of recurrence			
		High	Moderate	Low	Normal
High	15	8 (54)	5 (33)	0	2 (13)
Moderate	6	1 (17)	2 (33)	1 (17)	2 (33)
Low	5	1 (20)	2 (40)	1 (20)	1 (20)
Normal	15	2 (13)	1 (7)	0	12 (80)

AFP, α-fetoprotein. AFP values: high > 1000 ng/ml, moderate 100–1000 ng/ml, low 20–100 ng/ml; normal < 20 ng/ml. Values in parentheses are percentages

Table 5 *Recurrence detected at each year in patients with or without adjuvant chemotherapy after primary surgery for hepatocellular carcinoma*

Chemotherapy	No. of patients	Recurrence*				
		0·5–1 year	2 years	3 years	4 years	5 years
(+)	20	5/20 (25)	2/9 (22)	4/7 (57)	1/3 (33)	1/4 (25)
(−)	73	14/73 (19)	5/25 (20)	5/15 (33)	1/6 (17)	3/9 (33)

* Absolute number of patients developing recurrence/number eligible for each analysis. There was no statistically significant difference in the rate of recurrence at each year between the two groups. Values in parentheses are percentages

Table 6 *Patients surviving after detection of recurrences*

Groups	No. of patients	Survival*				
		1 year	2 years	3 years	4 years	5 years
I (Curative resection)	4	3/4 (75)	3/3 (75)	2/2 (75)	1/2 (38)	1/1 (38)
II (Palliative resection)	4	3/4 (75)	1/2 (50)	—		
III (Lipiodolization)	15	8/15 (62)	3/5 (44)	1/1 (44)	0/1 (0)	
IV (Systemic chemotherapy)	12	6/12 (50)	2/6 (17)	0/2 (0)		
V (No treatment)	5	1/5 (20)	0/1 (0)			

* Absolute number of patients surviving/number eligible for each analysis. Numbers in parentheses are survival rates, calculated according to the method of Kaplan and Meier[16]. One patient given radiation for a brain metastasis was excluded. One patient in 'Curative resection' is disease-free 9 years after the second operation

Table 7 *Changes in liver function at the time of primary and second operations in patients first treated with major hepatectomy*

Case	Age	Sex	Surgery*	Liver parenchyma	Duration between two operations (months)	Primary				Second			
						GPT	TB	ALB	ICG	GPT	TB	ALB	ICG
1	51	F	RL	Cirrhosis	26	45	0·6	3·9	7·1	50	0·5	4·1	10·0
2	34	M	RL	Fibrosis	27	223	0·6	4·3	8·1	131	0·9	4·5	8·1
3	51	M	LL	Cirrhosis	9	65	1·0	3·4	21·5	75	0·8	3·4	20·9

* Surgical procedure at primary operation. RL, right lobectomy; LL, left lobectomy, GPT, glutamic pyruvic transaminse (0–40 units/l); TB, total bilirubin (0·2–1·2 mg/dl); ALB, albumin (3·9–5·0 g/dl); ICG, (indocyanine green) retention test in 15 min (0–10 per cent); numbers in parentheses are normal ranges

1-, 3- and 5-year survival rates to be 83, 51, and 26 per cent, respectively.

In 4 of the 41 patients with a recurrence, a single or satellite nodules located near to the tumour were present in the remnant of the liver. These second tumours were detected between 5 and 29 months after primary surgery, by ultrasound in three patients and by elevated AFP concentrations in one. These four patients underwent partial hepatic resection (group I). Two of these four are living and are disease-free 9 years and 2 years and 9 months after the primary resection. One patient died of septic complications within 30 days after the second operation. The other died of liver failure 7 months after the third radical resection for a recurrence. Four patients underwent palliative re-resection (group II), one of whom was a case of fibrolamellar variant of HCC, and is living 29 months after the palliative second resection. Another patient is also living 19 months after palliative operation. The remaining two died of cancer 13 and 9 months postoperatively. The other 33 were not candidates for surgery, for the following reasons: anatomically advanced disease in 27, impaired hepatocellular function in 3 and poor clinical status in 3. Fifteen underwent Lipiodolization (group III) and systemic chemotherapy was also given to six of these fifteen. Systemic chemotherapy alone was prescribed for 12 (group IV). Radiation was given to the patient with brain metastasis. No treatment was given to five patients (group V) Cumulative survival rates after detection of the recurrence in each group are shown in *Table 6*.

Changes in liver function between initial and second operations second operations

Table 7 summarizes changes in liver function at the time of the first and second operations in patients in group I who underwent major resection. Values of serum glutamic pyruvic transaminase (GPT), total bilirubin, albumin and indocyanine green (ICG) retention test were much the same at the time of the two operations, even in those with cirrhosis.

Discussion

Intrahepatic recurrences after primary surgery for HCC are frequent. Since the portal vein is the draining vessel of HCC, invasion is more common in the portal than in the hepatic vein[17]. The presence of tumour thrombi in the portal vein was one factor significantly influencing survival after resection[18]. For early detection of liver tumours, ultrasound is an excellent diagnostic tool[5,19]; in three of our four patients undergoing a second curative resection, sonography led to detection of recurrences. Ebara *et al.*[20] stated that the minimum interval calculated from the time necessary for detecting a 1 cm increase in a 2 cm HCC by ultrasound was 3 months. This suggests that more frequent scanning may aid detection of a recurrence.

Serial measurement of serum AFP before and after presumably curative surgery of HCC is helpful in the management of these patients[21]. Nevertheless, the levels of this tumour marker in the sera of patients with HCC did not always show the same ranges seen before the primary surgery and at the time of recurrence. AFP thus appears to be a non-specific, unreliable test for such patients. Possible explanations for this phenomenon are as follows· (1) Kojiro *et al.*[22] demonstrated histochemically that there was a variation in AFP synthesis in different parts of the same tumour. AFP ranges might change at the time of recurrence due to the nature of unrecognized cancer cells remaining after an incomplete resection. (2) The nature of the tumour may change with growth[23]. (3) It is possible that recurrences were new primary tumours[24] with different characteristics.

Foster and Berman[25] reported in the 1974 Liver Tumour Survey that 1-, 3- and 5-year survival rates after curative resection for HCC in 101 patients were 80, 53 and 30 per cent, respectively. In 1981, Adson and Weiland[10] showed that 3- and 5-year survival rates in 44 patients with primary malignant hepatic tumours were 65 and 36 per cent, respectively. In Japan, Okuda *et al.*[8] reported in 1984 that 1-, 2- and 3-year survival rates after surgery in 98 patients were 65, 43 and 34 per cent, respectively. The results in our patients undergoing primary curative hepatic resections were comparable to those reported from Western countries, and slightly better than those from other institutes in Japan.

Although surgery for liver cancer has made great strides and the survival rates for these patients have improved[11,12], our study confirmed the dismal prognosis for the majority of patients with HCC. Fewer than 10 per cent of the original 570 patients surviving were disease-free at the time of the analysis. Long-term survival depends on total excision of a tumour from the liver. Early detection is therefore of prime importance in the treatment of HCC. In those undergoing hepatic resection, a major problem is the prevention or treatment of tumour recurrence. In the present study, adjuvant cancer chemotherapy with oral administration of 5-FU had no preventive effect on recurrence, though this was not a prospective randomized controlled study. Such a study is in progress in a multicentre trial in Japan.

In patients with a recurrence, long-term survival was achieved only for those who underwent a second radical resection, and similar findings were reported by Nagasue *et al.*[26]. The results in this study showed that liver function was not deranged at the time of second hepatic resection, even in cirrhotic patients who had undergone a wide excision of the liver at the time of primary operation. Thus, a careful follow-up with the use of multidiagnostic modalities to detect recurrences at an early stage are important. After early detection of a recurrence, the rate of liver re-resection which offers the prospect of long-term survival is much increased.

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Necrosectomy and postoperative local lavage in necrotizing pancreatitis

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Necrosectomy with postoperative continuous local lavage was performed in a prospective study involving 95 patients with necrotizing pancreatitis. In the same period 567 patients with oedematous-interstitial pancreatitis were treated non-operatively with a hospital mortality rate of 0·7 per cent. In patients with necrotizing pancreatitis the median Ranson criteria score was 4·5 points; operation was required at a median of 7 days after the onset of symptoms because of non-response to conservative treatment. In all, 59 per cent of the patients (56 out of 95) developed extended intrapancreatic parenchymal necrosis, 70 per cent had ascites, and 66 per cent had intra- and extrapancreatic necrosis; 42 per cent of the patients had bacterial infection of the necrotic tissue. For lavage a median of 8 l/24 h of fluid were instilled postoperatively for 25 days (median). The lavage fluid showed high levels of immunoreactive trypsin, phospholipase A_2*, and endotoxin in the early postoperative period. Hospital mortality rate was 8·4 per cent. Necrosectomy and continuous postoperative lavage can achieve high survival rates in patients with necrotizing pancreatitis. Postoperative local lavage allows the continuous non-operative evacuation of biologically active compounds and devitalized tissue, and avoids damage to remaining vital exocrine and endocrine pancreatic tissue.*

Keywords: Necrotizing pancreatitis, necrosectomy, local lavage

Morphologically, acute pancreatitis includes oedematous-interstitial and necrotizing forms of pancreatic inflammation. Necrotizing pancreatitis remains a severe disease with high morbidity and mortality. Clinical studies suggest that the necrotizing form of the disease involves between 5 and 16 per cent of all patients with acute pancreatitis[1–4] and that morbidity and mortality are directly related to the extent of intrapancreatic parenchymal necrosis, to the development of extrapancreatic retroperitoneal fat necrosis and, most importantly, to bacterial contamination of the necrosis[5–8].

Many experimental and clinical data indicate that there is liberation of active enzymes[9–11], vasoactive substances[12–14], and toxins[15] in the peripancreatic, retroperitoneal and intraperitoneal fluids during the acute inflammation. These bioactive compounds are disseminated following their direct transfer into the portal circulation and pass into the systemic circulation via the thoracic duct[16]. Results from animal and clinical studies indicate that there is a relationship between the peripancreatic and intraperitoneal liberation of vasoactive and toxic substances and the frequency of cardiocirculatory, pulmonary, and renal organ dysfunction early in the course of acute pancreatitis[6,17–20]. The later period of acute pancreatitis may be dominated by the bacterial contamination of the necrosis, which causes local and systemic septic complications.

In order to improve the prognosis of patients with necrotizing pancreatitis we have applied a combination of two measures, namely necrosectomy and continuous local lavage. The present study describes their efficacy in the management of this severe disease.

Patients

In the period May 1982 to June 1987, 744 patients with acute pancreatitis were admitted to our unit (*Table 1*). Five hundred and sixty-seven patients deemed to have oedematous-interstitial pancreatitis were successfully treated conservatively, sixty-nine of them with additional biliary surgery; the mortality rate of this group of patients was 0·7 per cent.

Pancreatic necrosis—which in most cases was verified by contrast-enhanced computed tomography (cCT)[21]—complicated the course of the disease in 130 patients. Twenty of these patients with predominantly minor necrotic areas were maintained on conservative treatment with two deaths due to shock in patients who had developed more extended necrosis. Of these 130 patients, 110 underwent surgical treatment; 95 of them were included in a prospective clinical trial and were subjected to necrosectomy and postoperative continuous local lavage Fifteen patients with less severe disease, who were treated by pancreatic resection (three patients) or local drainage (twelve patients), were excluded from this study; two of these patients died, one of massive diffuse haemorrhage as a consequence of a deranged haemostasis in association with advanced liver cirrhosis, and the other of septic shock after transfer from another hospital with severe intra-abdominal sepsis and fascial disruption after laparotomy.

Likewise, 14 patients with pancreatic abscess and 33 patients with pancreatic pseudocysts were excluded from further consideration. Of the 95 patients included in the prospective study of necrotizing pancreatitis, 60 were men and 35 women. The median age was 48 (18–89) years. Of the common aetiological factors, alcohol abuse was present in 41 patients (43 per cent), gallstones in 25 (26 per cent), and both conditions in 5 patients (5 per cent). Eight patients (9 per cent) had

Table 1 *Forms of acute pancreatitis encountered in 744 hospitalized patients*

	Patients		
Type of disease	Total	Surgical management	% of total
Oedematous-interstitial	567	—	76·2
Necrotizing	130	110	17·5
Pancreatic abscess	14	14	1·9
Pseudocysts	33	33	4·4

Part of the data have been presented orally at the Golden Jubilee of the British Society of Gastroenterology, London, 15–18 September 1987

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Table 2 *Pre-operative morbidity in 95 patients with necrotizing pancreatitis*

	Patients	
	n	%
Pulmonary dysfunction	56	59
Renal dysfunction	35	37
Shock	18	19
Sepsis*	26	27
Ileus	22	23
Gastrointestinal bleeding	11	12

* Rectal temperature $>38{\cdot}5°\text{C}$ + leucocytes $<4000/>12\,000/\text{mm}^3$ and platelets $<150\,000/\text{mm}^3$ + metabolic acidosis (base excess >-4 mmol/l)

suffered from abdominal trauma while none of these conditions was present in the remaining 21 patients (22 per cent)

Of the 95 patients, 35 (37 per cent) were admitted within 24 h of the onset of their complaint. The mean duration of symptoms before admission was 1·5 days At the initial examination all patients complained of severe abdominal pain and tenderness Guarding and nausea were present in two-thirds of the patients The serum amylase concentration was elevated in 90 per cent of the patients. The initial assessment of early prognostic signs[22] which were reduced to ten (out of eleven Ranson criteria) by omitting estimated fluid sequestration revealed a median value of 4·5 points.

Pre-operative morbidity

At the time of admission or during the following course most of the 95 patients developed single or multiple systemic complications (*Table 2*). A fall in arterial oxygen pressure below 60 mmHg was recorded in 59 per cent of the patients and was taken as a sign of pulmonary dysfunction, a third of these patients required mechanical ventilation A rise in the serum creatinine concentration above normal (1 4 mg/dl) was found in 37 per cent of the patients. Nineteen per cent developed circulatory shock (as defined by a systolic blood pressure of less than 80 mmHg for at least 15 min) and 27 per cent developed signs and symptoms of generalized sepsis. Paralytic ileus was diagnosed in 23 per cent and pleural effusion in 36 per cent.

Clinical management

In the first instance, all patients were treated conservatively with nasogastric intubation, intravenous crystalloid administration, plasma and albumin substitution where necessary, and procainamide infusion for analgesia. In cases of multiple organ failure, cardiocirculatory monitoring was supplemented by a Swan-Ganz catheter[6]. Oxygen was administered by nasal tube or, if arterial oxygen pressure fell below 50 mmHg, by mechanical ventilation. Renal insufficiency was treated with adequate fluid substitution and dopamine as required. Half of the patients who developed signs of sepsis were given antibiotics If these steps did not effect evident clinical improvement within 3 days, surgical intervention was considered to be the treatment of choice to prevent irreversible organ damage and a lethal course *Table 3* shows the indications for operative management These were predominantly increasing systemic complications (78 patients) and/or an acute surgical abdomen (54 patients) which were combined in 51 patients In all, 26 of these patients suffered from generalized sepsis. In 14 patients persisting or increasing abdominal symptoms combined with fever and leucocytosis were taken to indicate the need for surgical treatment In addition to these clinical criteria the diagnosis of necrotizing pancreatitis was obtained in 59 (83 per cent) of 71 patients subjected to a cCT examination. The overall duration of conservative therapy before taking the decision to perform an operation was 5 days, while the median duration from the onset of the illness was 7 days.

Pre-, intra-, and postoperative measurements

Endotoxin. Serum endotoxin levels were determined in 30 patients before operation and endotoxin levels were measured in ascitic fluid collected intra-operatively in 28 patients[23]. Two classes of severity were formulated· low level endotoxin concentration was an endotoxin level of up to 10 units/ml; high levels were values above 10 units/ml.

Pancreatic isoamylase, trypsin. Isoamylase and trypsin concentrations were determined pre-operatively in the serum, and intra-operatively in the ascitic fluid of 18 patients (Isoamylase Test Phadebas, Pharmacia Uppsala, Sweden, and RIA-Gnost-Trypsin, Behring Werke Marburg, FRG). The normal serum values of isoamylase are below 240 units/l, and those of trypsin below 446 ng/ml.

Phospholipase A_2. The concentrations of immunoreactive pancreatic phospholipase A_2[24] and the phospholipase A_2 activity[25] were determined in intra-operative samples of ascitic fluid of 37 and 29 patients, respectively The normal serum values are below 10 ng/ml and 2 units/l respectively.

Bacteriological assessments Specimens from several portions of the necrotic tissue were submitted to the bacteriological laboratory for standard culture and sensitivity determinations.

Intra-operative findings

The extent of the necrosis in head, body, and tail of the pancreas was assessed thoroughly and classified into four degrees on the basis of the wet weight of the extracted necrotic tissue as described elsewhere[5]. Since digital necrosectomy was preferred to the use of instruments in order to save vital tissue, only clearly demarcated necrotic tissue was removed. However, histological examination of the removed necrotic debris revealed that some necrotic fatty tissue was included with parenchymal necrotic material in 78 per cent of patients Thus, the categories used are approximations only. The extent of pancreatic necrosis in the studied patients was categorized as focal (wet weight <50 g) in 39 patients, as extended (wet weight 50–120 g) in 32 patients, and as subtotal (>120 g) or total (>190 g) in 24 patients Pancreatogenous ascites was more common with more extensive pancreatic necrosis, similarly extrapancreatic spread was significantly related to extended pancreatic necrosis (*Table 4*). The bacteriological investigation of necrosis samples from 89 patients revealed bacterial growth in the necrosis of 42 per cent of the patients. The prevailing micro-organisms were Gram-negative intestinal bacteria, mainly *Escherichia coli.* Bacterial infection was significantly more common in extended than in local necrosis The hospital mortality rate was related to the extent of pancreatic necrosis (*Table 5*).

Surgical technique

After removing all necrosis while carefully conserving perfused pancreatic tissue and ensuring haemostasis by means of transfixion stitches using 4–0/5–0 Prolene (Ethicon Ltd, UK), two double-lumen 24 Charrière tubes (Argyle, FRG) were inserted through separate incisions with their tips in the necrosis cavity. The gastrocolic and duodenocolic ligaments were then sutured to provide a separate lavage compartment In addition, for short-term peritoneal dialysis (1–3 days) a Tenckhoff catheter (Boehringer Ingelheim, FRG) was placed in either the left or the right hypogastrium in 56 patients. For lavage, a slightly hyperosmotic fluid was used (CAPD, Fresenius, FRG)

Further surgical measures were required in 25 patients Cholecystectomy was performed in 18 patients In three patients involvement of the spleen or its vessels in the necrotizing process necessitated splenectomy. Other procedures were performed in seven patients

Table 3 *Indications for surgical management in 95 patients with necrotizing pancreatitis*

	Patients	
Complications during intensive care treatment	*n*	%
Acute abdomen	3(54)	3‡
Severe systemic complications	78	82
Sepsis*	26	27
Organ dysfunction	54	57
Pulmonary ($P_{a,O_2}<60$ mmHg)	52	55
Renal (serum creatinine $>1{\cdot}4$ mg/dl)	29	30
Cardiocirculatory (systolic BP <80 mmHg $\geqslant 15$ mm)	16	17
Metabolic insufficiency (blood glucose >200 mg/dl; serum calcium <2 mmol/l)	54	57
Persisting/increasing local complications†	14	15

* Rectal temperature $>38{\cdot}5°\text{C}$ + leucocytes $<4000/>12\,000/\text{mm}^3$ and platelets $<150\,000/\text{mm}^3$ + metabolic acidosis (base excess >-4 mmol/l). † Palpable tumour + persisting pain >8 days in spite of analgesia + rectal temperature $>38{\cdot}5°\text{C}$ + leucocytes $>16\,000\,\text{mm}^3$. ‡ The total incidence of acute abdomen was 54 patients

Table 4 *Intra-operative evaluation of the necrotizing process in 95 patients*

	Ascites		Extrapancreatic necrosis		Bacterial contamination*	
Degree of pancreatic necrosis	*n*	%	*n*	%	*n*	%
Focal ($n=39$)	22	56	19	49	12 (38)	32
Extended ($n=32$)	23	72	28	88	17 (29)	59
Subtotal/total ($n=24$)	21	88	16	67	8 (22)	36
Total number of patients ($n=95$)	66	70	63	66	37 (89)	42

* 89 patients studied

Table 5 *Hospital mortality in patients with infected and non-infected necrotizing pancreatitis after necrosectomy and local lavage*

	Bacterial culture positive (37 patients)			Bacterial culture negative (52 patients)		
		Mortality			Mortality	
	n	*n*	%	*n*	*n*	%
Focal necrosis ($n=38$)	12	1	8	26	1	4
Extended necrosis ($n=29$)	17	2	12	12	0	—
Subtotal/total necrosis ($n=22$)	8	2	25	14	2	14
Total number of patients 89	37	5*	14	52	3**	6

* Five patients dying of sepsis

** Two patients dying from massive diffuse local bleeding and one from cardiogenic shock

Table 6 *Pancreatic enzymes and endotoxin levels in intra-operative samples of peritoneal fluid*

	Isoamylase	Immunoreactive trypsin	Immunoreactive phospholipase A_2	Phospholipase A_2 activity	Endotoxin
No. of patients tested	18	18	37	29	28
No. of patients with pathological values	12	12	28	19	17
Median	2362 units/l	2412 ng/ml	63·2 ng/ml	4·2 units/l	20 units/ml
Range	5–12 600 units/l	2–12 740 ng/ml	0·8–359 ng/ml	0·1–185 units/l	5–2400 units/ml

Lavage technique

Local lavage was performed for a median of 25 (range 3–90) days, and a median of 8 (range 4–20) litres of fluid were instilled per 24 h. The criteria for stopping lavage were absence of any signs of acute pancreatitis and complete cleansing of the necrosis cavity. This could be confirmed by measuring isoamylase and trypsin levels in the lavage fluid, assessing the sterility of the fluid, and noting the recovery of little or no devitalized tissue (< 7 g/24 h).

Both the duration and amount of lavage fluid used correlated significantly with the extent of the pancreatic necrotizing process. Local lavage was required for 13, 30, and 49 days in patients with focal, extended, and subtotal/total necrosis, respectively. The amount of fluid required for cleansing the pancreatic bed averaged 6 litres in those with focal necrosis and 8 litres in those with more extensive necrosis.

Results

Treatment

On average, patients had a total pre- and postoperative stay in the intensive care unit of 7 days. Twenty-six patients (27 per cent) had to undergo reoperation: 23 of them had developed a secondary abscess in the area of the original necrosis cavity, massive diffuse local bleeding was responsible in one patient, one developed progressive necrosis, and another developed a colonic fistula leading to intra-abdominal sepsis. Pancreatic fistulae were observed in 10 more patients, but in all cases they closed spontaneously. Local complications were proportional to the extent of the intrapancreatic parenchymal necrosis; thus 7 patients (18 per cent) with focal necrosis, 9 patients (28 per cent) with extended necrosis, and 10 patients (42 per cent) with subtotal/total pancreatic necrosis required reoperation.

Organ complications were rare in the postoperative course and occurred in 16 patients, mainly in connection with local complications and reoperation. Ten of these patients had suffered failure of one or more organs before operation. Of 39 patients who had normal pre-operative pulmonary function, 7 developed postoperative pulmonary insufficiency; 4 of 60 patients developed renal insufficiency, 3 of 77 patients developed circulatory insufficiency, and 9 of 69 patients developed generalized sepsis. The hospital stay of surviving patients came to a median of 65 (range 16–150) days. Eight patients died following operation. The cause of death was sepsis in five patients, massive diffuse local haemorrhage in two, and cardiogenic shock in one patient. Mortality was related to both the extent of necrosis and the presence of bacterial infection in the necrosis (*Table 5*). The three deaths in patients with sterile necrosis supervened on a fulminant pre-operative course with patients showing 8–10 positive early objective signs as described by Ranson.

Measurements

Enzyme measurements. The biochemical investigations of pancreatogenous ascites revealed enzyme levels to be considerably elevated in the majority of patients (*Table 6*). The median value for pancreatic isoamylase in the measured patients was ten times the normal serum value. Median immunoreactive trypsin values were up to five times the normal level. Both enzymes were pathologically increased in 67 per cent of cases. Immunoreactive phospholipase A_2 was increased in 76 per cent and the median value was more than seven times the normal level; phospholipase A_2 activity was elevated in 66 per cent and the median value was twice the normal level.

Endotoxin measurements. The pre-operative endotoxin levels in the peripheral blood were elevated in 21 (70 per cent) of 30 measured patients. The levels were above 10 units/ml in 10 patients (48 per cent). Intra-operative ascites samples were positive for endotoxin in 17 (61 per cent) of 28 measured patients, and the levels exceeded 10 units/ml in 13 patients (76 per cent), the peak value amounting to 2400 units/ml.

Discussion

The term 'acute pancreatitis' can be taken to comprise four different entities on the basis of morphological and clinical criteria: oedematous-interstitial pancreatitis, necrotizing pancreatitis—with sterile or infected necrosis, pancreatic abscess, and pancreatic pseudocyst. Characteristic features of oedematous-interstitial pancreatitis are a periacinar and peripancreatic oedema and an interstitial accumulation of inflammatory cells. The clinical course is mostly mild and self-limiting, and with conservative treatment the patients are usually free of pain after a few days; hospital mortality is usually below 1–2 per cent. Additional features of the necrotizing type of acute pancreatitis are the development of acinar cell necrosis with intrapancreatic and peripancreatic haemorrhage as well as fat necrosis in the intrapancreatic, peripancreatic, and often retropancreatic fatty tissue areas. From a clinical point of view, patients with necrotizing pancreatitis frequently suffer from a severe disease with persisting abdominal pain, abdominal tenderness and persisting fever and hypovolaemia.

Early in their clinical course patients with necrotizing inflammation frequently develop cardiocirculatory, pulmonary, renal and hepatic organ dysfunctions and gastrointestinal complications, as shown in the patients of this study. In about 40 per cent of necrotizing pancreatitis patients, bacterial contamination of the necrosis takes place and may occur at an early stage of the disease. The contamination rate of the present study group was 42 per cent while 66 per cent showed extrapancreatic necrosis at operation and 70 per cent had ascites; however, only half of the ascitic patients had haemorrhagic ascites.

Patients with infected necrosis significantly more often develop organ complications than patients with sterile necrosis[1]. Patients with infected necrosis mostly have a septic course[1,26,27] and their hospital mortality exceeds 30 per cent in most reported series. As shown recently, morbidity and mortality are considerably higher in patients with infected necrosis[1,5]. It has become evident that morphological changes *per se* have less influence on the course of the disease than the presence of bacteria in the necrotic tissue.

Pancreatic abscess is usually a late consequence of acute pancreatitis. It develops after the acute inflammation has subsided, usually 4–6 weeks after the acute attack. Such patients have a localized collection of pus, which can be within or outside the pancreas and which is surrounded by a more or less distinct and newly formed wall of inflammatory tissue[26]. To clarify the terminology, we suggest that only the terms 'infected necrosis' and 'pancreatic abscess' should be used to describe the two different forms of infection in acute pancreatitis. 'Major pancreatic infection'[28], 'peripancreatic infection' or 'peripancreatic sepsis'[29], 'phlegmon'[30] or 'infected pancreatic abscess'[31] are confusing terms and in our view should be avoided.

Pseudocysts that complicate acute pancreatitis usually develop as a late consequence some weeks or months after necrotizing pancreatitis. They may be inside the pancreas or in the peripancreatic region and can contain pancreatic fluid with a high concentration of enzymes, sterile necrotic debris or infected material.

One of the main characteristics of acute pancreatic inflammation is the exudation of enzyme-rich fluid and proteins in and around the pancreas and into the peritoneal cavity. In experimental haemorrhagic pancreatitis, ascites accumulates within a few hours of induction[32–34]. In human disease retroperitoneal and intraperitoneal fluid accumulation is also observed early in the course of the disease, especially in patients with extensive necrotizing inflammation. The retroperitoneal and intraperitoneal pancreatic fluids consist of various biologically active compounds. In several clinical studies, mostly including a small number of patients with necrotizing pancreatitis, activated proteases such as trypsin, chymotrypsin and elastase 2 have been found in ascites[17,35]. Others have found a high ascitic content of bradykinin, kininogen, and degradation products of C3[9,12,13]. In the present study endotoxin was detected in the ascitic fluid of 17 of the 28 tested patients, and 76 per cent had a high concentration. A high concentration of pancreatic immunoreactive phospholipase A_2 was found in 28 of 37 measured patients and in 19 of 29 patients a high phospholipase A_2 activity was also observed. It has been shown recently that amylase, trypsin, and phospholipase A_2 are present in increased amounts in the peritoneal fluid up to the 12th to 14th day after surgical treatment[2]. From this observation it is concluded that biologically active substances are liberated for about 2–3 weeks after necrotizing pancreatitis has occurred[2]. The systemic delivery of these bioactive compounds takes place by direct transfer to the portal circulation and from the retroperitoneal and peripancreatic spaces via the thoracic duct[34]. There is strong evidence linking the presence of these bioactive compounds in the systemic circulation with an increased occurrence of organ failure in patients with necrotizing pancreatitis[15,36].

Any medical or surgical management of patients with necrotizing pancreatitis should be directed towards removal of devitalized intra- and extrapancreatic tissue and to the opening, emptying, and drainage of intra- and extrapancreatic fluid collections. Another important goal of surgical treatment is the prevention of the systemic spread of these vasoactive and toxic substances originating from the necrotizing process[2]. However, controlled clinical trials have shown no decrease in the morbidity and mortality of patients with acute haemorrhagic pancreatitis given prolonged dialysis treatment[37,38]. While peritoneal dialysis in patients with necrotizing inflammation empties the peritoneal cavity, it does not affect the necrotic tissue, the bacterially contaminated areas, or the retroperitoneal fluid collections and their content of toxic and vasoactive substances. Consequently, after discontinuation of the peritoneal lavage many patients may have died from the late sequelae of pancreatitis caused mainly by the retroperitoneal collection of necrotic tissue and its bacterial infection.

A radical approach for interrupting the necrotizing process was favoured particularly by French surgeons who performed left pancreatic resection or even total pancreatectomy. Resection in the severely inflamed areas, however, resulted in high complication rates. Mortality came to an average of 41 per cent in a total of 192 patients treated in several studies by resection techniques[39,40]. Resection of the pancreas in cases with acute necrotizing pancreatitis is associated with a high operative risk. Pancreaticoduodenectomy is a major surgical trauma in itself and adds to the high morbidity associated with the necrotizing process. Furthermore, major resection in necrotizing pancreatitis neglects the generally accepted surgical experience that in most cases there is vital, recoverable tissue between the necrotic areas[41]. The use of resection, which cannot be applied as a standard surgical procedure in the presence of retro- and intraperitoneal necrotizing inflammation, means that the patient is being overtreated. Even for those patients with so-called total pancreatic necrosis, surgical pancreatectomy is difficult to justify, because an intra-operative distinction between fat necrosis and necrosis of the pancreatic parenchyma cannot be made on the basis of macroscopic criteria alone. Therefore, resection in patients with necrotizing pancreatitis is an inadequate surgical procedure when compared with necrosectomy. Necrosectomy, as performed in this group of patients, means surgical removal of devitalized peri- and intrapancreatic tissue and emptying of intra- and peripancreatic and retroperitoneal fluid collections. The combination of necrosectomy and postoperative local lavage of the lesser sac provides an atraumatic and continuous evacuation of devitalized tissue as well as removing bacterially contaminated dead tissue and biologically active substances. As shown recently, continuous local lavage in the later postoperative period allows a safe, non-surgical evacuation of devitalized tissues without the need for routine reoperation or open packing[7,42,43]. This technique guarantees that areas with intact vascular perfusion are spared. The mechanical 'flow-through' technique after necrosectomy preserves vital pancreatic tissue and lowers the risk of major bleeding after surgery.

Debridement alone or in combination with drainage is an inadequate approach in patients with pancreatic necrosis, but is efficient in patients with pancreatic abscess[43,44]. The release of biologically active substances into the peripancreatic area after surgical debridement and the further development of devitalized tissue masses require continuous cleansing to prevent local septic complications. Using biological, biochemical and mechanical purification criteria for the termination of lavage, an average period of 25 postoperative days was required in the present study. Complications in the postoperative course, which arose predominantly from abscess formation, were due to dislocation or extrusion of parts of the lavage device. In general, surgery is indicated in patients with a necrotizing course if signs of an acute abdomen develop. Patients with severe acute pancreatitis who, in spite of maximum intensive care treatment over a period of at least 3 days, show increasin organ dysfunction and/or local or systemic septic complications, are also candidates for surgical treatment.

Morphological criteria can now be defined by repeated cCT investigations[21] in patients with extended intrapancreatic parenchymal necrosis or the combination of intra- and extrapancreatic necrosis. Furthermore, infected necrosis can now be confirmed by ultrasound-guided needle aspiration[45] identifying patients who will benefit from surgical management. We believe that patients with sterile focal pancreatic necrosis do not need surgical management as local or systemic complications are rare in the course of the disease.

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Case report

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Patient controlled analgesia and urinary retention

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The phenomenon of urinary retention after surgery is well recognized. We would like to report 2 instances where patients using patient-controlled analgesia (PCA) had undiagnosed urinary retention leading to the consumption of large amounts of morphine. Since the first description of PCA by Sechzer in 1968[1] many studies have been undertaken to demonstrate its use and effectiveness in the management of postoperative pain[2]. In the Department of Surgery, Royal Infirmary, Glasgow, many patients who are scheduled to undergo major abdominal surgery use PCA postoperatively. Our PCA systems use morphine in a dilution of 100 mg in 1 litre normal saline, and at each successful demand for analgesia, the patient receives a bolus dose of 0·02 mg/kg intravenously[3] A 50 kg patient will therefore receive a bolus dose of 1 mg in a volume of 10 ml.

Case report

Two fit male patients presented for upper abdominal surgery and each consented to enter into studies involving PCA for the first 24 h postoperatively. Both patients complained of severe abdominal pain during the evening following surgery and claimed that they were not obtaining adequate relief despite having received large amounts of morphine Neither patient could locate the source of pain exactly, but further examination revealed that each had a distended bladder. The patients did not complain of urgency, but they both experienced great difficulty in subsequently emptying their bladders The volume of urine obtained was greater than 600 ml in each case. On evacuation of the bladder, each patient experienced virtually complete relief of pain, and their subsequent morphine consumption was greatly reduced (*Table 1*).

Table 1 *Patient data and morphine consumption for the 4-h periods before and after passing urine*

	Patient 1	Patient 2
Age (years)	22	29
Weight (kg)	59	60
Operation	LCS	C
Time to pass urine (h)	14·5	8·5
Morphine consumption 4 h before urination (mg)	26·4	20·4
Morphine consumption 4 h after urination (mg)	6·6	4·8
Total morphine consumption (mg in 24 h)	110·6	94·8

LCS, lesser curve seromyotomy; C, cholecystectomy

Discussion

The reasons for the problems encountered in these patients are varied and complex. Morphine acts on the detrusor muscle of the bladder to promote the sensation of urgency, but the central effect of morphine may make the patient inattentive to this sensation. It also increases sphincter tone to make urination difficult[4,5].

The sequence of events for these patients may have been that initially the morphine was used with good effect to relieve wound pain but subsequently the awareness of urgency was reduced. Bladder distension may have resulted in abdominal discomfort which was not reduced by further doses of morphine. A cycle would therefore have been established of increasing bladder volume and distension, increasing discomfort and increased morphine consumption. Despite the large amounts of morphine consumed by the patients, none was considered to be at risk of respiratory depression. However, the possibility that unrecognized bladder distension leading indirectly to respiratory depression could occur if patients have a large depot of narcotic available to them.

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Biochemical prediction of gallstones in acute pancreatitis: a prospective study of three systems

Three clinicobiochemical systems have been proposed for predicting gallstones in acute pancreatitis based on one, three and five factors respectively, but have not been compared in a single prospective study. System 1 is based on the serum transaminase alone; system 2 uses alkaline phosphatase and bilirubin in addition to transaminase; and system 3 involves female gender, age, amylase and alkaline phosphatase in addition to transaminase. Over the 4-year period 1983–86, 368 patients with 391 episodes of acute pancreatitis had clinicobiochemical analysis within 48 h. Of these episodes, 220 were related to gallstones (56 per cent), 62 to alcohol (16 per cent) and 109 to other aetiologies or were idiopathic (28 per cent). Significant differences were found between the biliary and non-biliary groups with respect to sex (139 versus *59 women,* $P<0{\cdot}002$*), age (65±17* versus *52±19 years,* $P<0{\cdot}0001$*) and serum amylase (6041±6335* versus *4546±3990 units/l,* $P<0{\cdot}0001$*), alkaline phosphatase (257±225* versus *141±137 units/l,* $P<0{\cdot}0001$*), alanine transaminase (221±227* versus *72±119 units/l,* $P<0{\cdot}0001$*) and bilirubin (40±39* versus *24±30 µmol/l,* $P=0{\cdot}0001$*). The sensitivity and specificity was 75 per cent and 74 per cent for the one-factor system, 74 per cent and 78 per cent for the three-factor system and 62 per cent and 80 per cent for the five-factor system. The predictive value of a positive result was 78·8 per cent, 81·5 per cent and 80·1 per cent and of a negative result 69·4 per cent, 70·1 per cent and 62·3 per cent for the three systems respectively. The performances of the one- and three-factor systems were marginally better than that of the five-factor system; the one-factor system, however, had the advantage of simplicity.*

Keywords: Acute pancreatitis, gallstones, biochemical tests

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The early detection of gallstones in acute pancreatitis is essential, whether urgent decompression of the biliary tree by surgical[1,2] or endoscopic[3–5] means is being considered, or a policy of early cholecystectomy[6] is being practised. Biochemical analysis for the prediction of gallstones is simple, widely available and may be carried out irrespective of the clinical state of the patient. Three systems for the clinicobiochemical detection of gallstones in acute pancreatitis have been proposed based on the sex and age of patients and the serum level of amylase, bilirubin, alkaline phosphatase and alanine/aspartate transaminase estimated within 48 h of admission to hospital (*Table 1*)[7–9]. The reported sensitivities of these systems is 73–86 per cent. Their lack of specificity prohibits their use as the sole means of detecting gallstones in acute pancreatitis; they may, however, allow the selection of patients who require urgent investigations. The three proposed systems have not previously been compared in a single prospective study.

Patients and methods

Over a 4-year period from January 1983 to December 1986, 368 patients were admitted to hospitals in the Leicester area with 391 episodes of acute pancreatitis. These patients had not been studied previously for the purpose of assessing systems of gallstone prediction in acute pancreatitis; 170 were male and 198 female, with ages ranging from 14 years to 96 years (median 62 years). The diagnosis of acute pancreatitis was based on a serum amylase >1000 units/l (Phadebas) with a compatible clinical picture. Biochemical analysis was carried out within 48 h of admission to determine the serum levels of bilirubin, alkaline phosphatase and alanine transaminase using the Technicon SMAC 1 autoanalyser.

The presence of gallstones was determined by the unequivocal findings at ultrasonography, oral cholecystography or endoscopic retrograde cholangiopancreatography and, where possible, confirmed by operative or post-mortem findings. Patients without gallstones had a careful history taken to assess alcohol consumption, serum calcium levels and fasting blood lipid assays. Patients termed 'idiopathic' by the referring hospitals were divided into 'true idiopathics' if investigations for gallstones had included a laparotomy or endoscopic retrograde cholangiopancreatography (ERCP), and 'aetiology not established' if these investigations had not been undertaken. The patients were divided into a biliary group and a non-biliary group (alcohol, idiopathic and other aetiologies) depending on the results of the above investigations. The aetiology was then related to the three different biochemical systems for the prediction of gallstones (*Table 1*). A separate analysis was also carried out in which patients in whom investigations for gallstones had

Table 1 *Systems* for predicting gallstones*

System and criteria	Prediction
System 1 (reference 7)	Predicts the presence of gallstones
Aspartate/alanine transaminase >60 units/l	
System 2 (reference 8)	The presence of one or more criteria predicts gallstones
Alkaline phosphatase >225 units/l	
Aspartate/alanine transaminase >75 units/l	
Bilirubin >40 µmol/l	
System 3 (reference 9)	The presence of three or more criteria predicts gallstones
Female sex	
Age >50 years	
Amylase >4000 units/l	
Aspartate/alanine transaminase >100 units/l	
Alkaline phosphatase >300 units/l	

* All three systems involve the use of transaminase

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not been adequately undertaken ('aetiology not established') were excluded.

Statistical analysis was performed using the χ^2 and Mann–Whitney *U* tests and the predictive values of the three different systems in detecting gallstones were determined. Significance was assumed as $P<0·05$; marginal significance of $P=0·05$ to $P=0·10$ is also mentioned.

Results

Biochemical information was obtained on 368 patients with 391 episodes of acute pancreatitis. The aetiology is shown in *Table 2* and the number and nature of investigations on which the aetiology was based in *Tables 3* and *4*. Eleven patients (3 per cent) had a laparotomy (5) or post-mortem examination (6) with no prior investigations of the biliary tree. Of the 210 patients with biliary pancreatitis, 115 (54·8 per cent) had had elective cholecystectomy with confirmation of the aetiology being obtained. Eighty-two patients with 85 episodes of acute pancreatitis were considered idiopathic. Thirty-nine of these patients (48 per cent) had a normal ERCP or absence of gallstones confirmed at laparotomy. Of the remaining 43 patients (52 per cent), ultrasonography alone had been carried out in 23.

Significant differences were found between the biliary and non-biliary groups (*Table 5*) as regards the age and sex of the patients and the serum levels of amylase, alkaline phosphatase, bilirubin and alanine transaminase. The ability of the three systems for gallstone prediction are shown in *Table 6*. The sensitivity (i.e. the proportion of patients with gallstones so predicted) was significantly better for systems 1 and 2 compared with system 3 (1 *versus* 3, $\chi^2=7·67$, d.f. = 1, $P=0·0056$; 2 *versus* 3, $\chi^2=7·08$, d.f. = 1, $P=0·0078$). System 2 provided marginally more correct predictions than did system 3 ($\chi^2=2·83$, d.f. = 1,

Table 2 *Aetiology of acute pancreatitis*

Aetiology	Episodes ($n=391$)		Patients ($n=368$)	
Gallstones	220	(56·3%)	210	(57·1%)
Alcohol	62	(15·9%)	56	(15·2%)
Idiopathic	41	(10·5%)	39	(10·6%)
Aetiology not established	44	(11·3%)	43	(11·7%)
Pancreatic duct stricture	5	(6·1%)	1	(5·4%)
Hyperlipidaemia	4		4	
Postendoscopic sphincterotomy	3		3	
Post ERCP	2		2	
Trauma	2		2	
Chronic pancreatitis	2		2	
Pancreatic carcinoma	2		2	
Polyarteritis nodosa	1		1	
Systemic lupus erythematosis	1		1	
Duodenal Crohn's disease	1		1	
Histiocytic lymphoma	1		1	

Table 3 *Type of investigation performed in each diagnostic group*

Aetiology	Investigation: Ultrasound (No.)	(%)	Oral cholecystogram (No.)	(%)	ERCP (No.)	(%)
Biliary ($n=210$)	190	90	39	19	74	35
Alcohol ($n=56$)	54	96	23	41	18	32
Idiopathic* ($n=82$)	77	94	27	33	40	49
Other aetiologies ($n=20$)	10	50	2	10	11	55

* 'True' idiopathic plus 'aetiology not established'

Table 5 *Clinical and biochemical results*

Predictive factor	Group: Biliary ($n=220$)	Non-biliary ($n=171$)	*P*
Sex	139 females	59 females	<0·002
Age (years)	64·7 ± 16·6	52·3 ± 19·3	<0·0001
Amylase (units/l)	6041 ± 6335	4546 ± 3990	<0·0001
Alkaline phosphatase (units/l)	257 ± 225	141 ± 137	<0·0001
Alanine transaminase (units/l)	221 ± 227	71·9 ± 118·5	<0·0001
Bilirubin (μmol/l)	39·8 ± 38·6	23·7 ± 30·0	=0·0001

Values are means ± s.d.

Table 6 *Predictive value of the 3 different systems in indicating gallstones in all 391 attacks*

Predictive analysis	Prediction by: System 1	System 2	System 3	*P*
Number correctly predicted	291	297	276	*
Percentage correctly predicted	74·4	76·0	70·6	*
Sensitivity (%)	74·5	74·1	62·3	†
Specificity (%)	74·3	78·4	80·1	n.s.
Predictive value of a positive result (%)	78·8	81·5	80·1	n.s.
Predictive value of a negative result (%)	69·4	70·1	62·3	‡

* 2 *versus* 3, $P=0·089$; †1 *versus* 3, $P=0·0056$; 2 *versus* 3, $P=0·0078$, ‡2 *versus* 3, $P=0·093$, all other comparisons were not significant (n.s.)

Table 4 *Number of diagnostic investigations (ultrasound, oral cholecystography and ERCP) performed according to aetiology*

Aetiology	Number of investigations: 1 (No.)	(%)	2 (No.)	(%)	3 or more (No.)	(%)	Urgent laparotomy or post-mortem examination (No.)	(%)
Biliary ($n=210$)	115	55*	83	40	9	4	2	1
Alcohol ($n=56$)	18	32	28	50	7	13	3	5
Idiopathic† ($n=82$)	30	37	41	50	7	9	5	6
Other aetiologies ($n=20$)	4	20	9	45	6	30	1	5

* Percentages have been rounded to the nearest whole number
† 'True' idiopathic plus 'aetiology not established'

Table 7 *Revised predictive analysis of the systems in 348 patients excluding those in the 'idiopathic' group who had not undergone laparotomy or ERCP*

	Prediction by			
Predictive analysis	System 1	System 2	System 3	*P*
Number correctly predicted	260	262	244	n s
Percentage correctly predicted	74·7	75·3	70·1	n.s
Sensitivity (%)	74·5	74·1	62·3	n s.
Specificity (%)	75·0	77·3	83·6	*
Predictive value of a positive result (%)	83·7	85·0	87·0	n.s
Predictive value of a negative result (%)	63·6	63·9	57·2	n s

*1 *versus* 3, $P=0{\cdot}089$; all other comparisons were not significant (n.s.)

$P=0{\cdot}093$). There was no statistical difference at all between systems 1 and 2. 'Idiopathic' patients who had neither laparotomy nor ERCP were excluded and the systems again analysed (*Table 7*). In this instance there were no significant differences between any of the systems, except that system 3 had a marginally better specificity than system 1 ($\chi^2=2{\cdot}88$, d.f.$=1$, $P=0{\cdot}089$).

Discussion

Clinicobiochemical systems[7–9] provide a simple and rapid method of selecting patients with acute pancreatitis in whom the probable aetiology is gallstones and who require urgent investigation by ultrasonography or ERCP to confirm their presence[5,6,10,11].

The optimum timing of cholecystectomy in patients with acute biliary pancreatitis is controversial[1,6,12,13]. Urgent surgery within a few days of admission is associated with a high mortality[2] and recurrent episodes of acute pancreatitis are common if surgery is delayed[12]. The early confirmation of the presence of gallstones allows cholecystectomy to be carried out after remission of the acute attack but before discharge from hospital, which is safe and avoids recurrent attacks[6].

Although urgent surgery is generally contra-indicated in acute pancreatitis, patients with common bile duct stones impacted at the ampulla of Vater may benefit from urgent endoscopic biliary decompression[3–5]. The presence of prognostic criteria suggesting a severe attack of pancreatitis[14], in association with a serum bilirubin level $>40\,\mu$mol/l, most readily identifies this group of patients[15].

The clinicobiochemical systems of gallstone prediction may be of further value in deciding the management of patients with acute pancreatitis in whom initial biliary ultrasound scanning is normal or unsuccessful. A biochemical prediction of gallstone presence strongly indicates the need for further biliary ultrasonography during remission of the acute attack of pancreatitis, when the sensitivity is increased[10,11].

A second normal scan in patients with a severe attack of pancreatitis and gallstones predicted by biochemical testing would be a good indication for ERCP to be carried out during the same admission. In patients with a mild attack of pancreatitis and normal repeat ultrasonography, it may be appropriate to carry out ERCP following resolution of the attack. At this time endoscopic bile sampling and bile crystal analysis is also useful for detecting microlithiasis[16].

The comparative study of the three proposed systems for the detection of gallstones in acute pancreatitis has shown their sensitivity to be 62–74 per cent, slightly lower than that previously reported[7–9]. Using the data from all 391 attacks, systems 1 and 2 were significantly better in terms of sensitivity than system 3 (*Table 6*). System 2 was also marginally better than system 3 in terms of the correct number of predictions and the predictive value of a negative test than system 3. Although significant differences in the levels of γ-glutamyl transferase were found, its application did not improve the diagnostic accuracy of the systems.

The incidence of 'idiopathic' patients in this series was higher than a recently reported single-centre study from this area in which ERCP was routinely used[8]. This would suggest inadequacies in the method of investigation of these patients in some hospitals. Further analysis of the systems was therefore carried out excluding patients termed 'idiopathic' in whom an absence of gallstones had not been confirmed by laparotomy, post-mortem examination or ERCP. Surprisingly, this showed that there was no significant difference in performance between any of these systems.

Despite the limitations of clinicobiochemical predictive systems for gallstones in acute pancreatitis, we believe that they have a useful role. The single-factor system proposed by Mayer and McMahon[7] (alanine or aspartate transaminase >60 units/l) has the major advantage of simplicity and deserves wider adoption.

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Surgical morbidity and mortality in one hundred and twenty-nine patients with obstructive jaundice

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One hundred and twenty-nine jaundiced patients were operated upon for the relief of benign and malignant bile duct obstruction during a 10-year period, 1977–86. The overall mortality was 4·7 per cent but increased to 9·1 per cent in patients with a serum bilirubin >300 μmol/l. In all, 46·5 per cent of patients had a rise in postoperative creatinine but renal dysfunction occurred in only 4·7 per cent. Wound infection developed in 3·1 per cent of patients and appeared unrelated to infected bile; 3·9 per cent of patients were treated for postoperative septicaemic episodes. The low morbidity and mortality observed suggests that pre-operative biliary drainage need not be considered in routine surgical practice if simple measures to maintain urine flow and prevent postoperative sepsis are used.

Keywords: Surgery, obstructive jaundice, morbidity, mortality

Surgery for biliary tract obstruction is still associated with significant morbidity and mortality. In jaundiced patients reported mortality rates range from 4–43 per cent and may be adversely influenced by several factors[1,2]. Similarly, although reduced by prophylactic antibiotics, wound sepsis rates remain high after exploration of the common bile duct especially in the presence of jaundice[3]. Renal failure is a particular hazard and is associated with a poor prognosis[3,4]. A number of pre-operative factors predisposing to mortality and morbidity have been established[5,6] and there has been recent interest in the putative protective role of pre-operative drainage[1,7–9].

The clinical course in 129 consecutive patients, under the care of a single consultant, operated on for obstructive jaundice was reviewed. The study period extended over 10 years (1977–86). The aim was to report mortality and morbidity in patients with surgical jaundice in whom a consistent management policy to reduce infective complications and avoid renal failure was followed.

Patients and methods

Definitions

Postoperative mortality was defined as death in hospital or within 30 days, whichever was greater.

Wound infection refers to the discharge of pus or of a serous or sanguinous discharge that grew a pathogenic micro-organism. All patients who at follow-up reported a discharge from their wound were considered to have had an infected wound[10].

Intraperitoneal abscess was recorded when pus was drained, aspirated, or discharged from the peritoneal cavity or there was radiological, ultrasonic, or necropsy evidence of an intraperitoneal collection.

Intra-operative haemorrhage was defined as blood loss during operation requiring transfusion of two or more units of blood.

Postoperative haemorrhage was defined as haematemesis, melaena, blood loss from the abdominal wound or drainage sites occurring after postoperative day 2 and requiring transfusion of 2 or more units of blood.

Patients with normal renal function before surgery (serum creatinine <130 μmol/l) in whom the serum creatinine more than doubled its pre-operative value or exceeded 180 μmol/l postoperatively were termed to have had postoperative renal dysfunction[6]. Patients with impaired renal function before surgery (serum creatinine >130 μmol/l) in whom the serum creatinine increased by more than 100 μmol/l postoperatively were also recorded as having had renal dysfunction[6].

Patients

The case records of patients undergoing biliary tract or pancreatic surgery from January 1977 to December 1986 identified from a prospective computerized audit of all abdominal operations were reviewed. Data on diagnosis, operative procedures, antibiotic usage and anastomotic, wound and infective complications were recorded prospectively as part of the audit. One hundred and twenty-nine patients with surgical jaundice confirmed biochemically at the time of operation were studied.

There were 73 men and 56 women with a median age of 71 years (*Figure 1*). A total of 81 (62·8 per cent) patients had a benign cause for their obstructive jaundice and 48 (37·2 per cent) patients had malignant obstruction. The serum bilirubin at the time of operation was >300 μmol/l in 22 patients, 200–299 μmol/l in 16 patients and <200 μmol/l in 91. The distribution of disease processes resulting in biliary obstruction is shown in *Table 1*.

Pre-operative preparation

The biliary tree was visualized radiologically by routine ultrasonic scanning supplemented with either percutaneous transhepatic or retrograde cholangiography. Vitamin K was routinely given, intravenous fluids were commenced on the evening before operation and, since 1983, oral sodium deoxycholate was administered for 48 h before surgery.

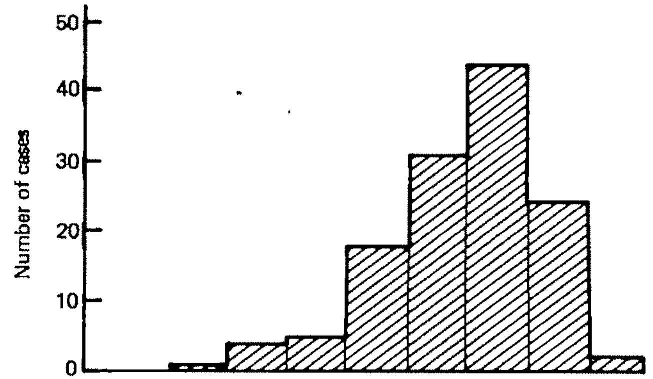

Figure 1 *Age distribution of 129 patients*

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Table 1 *Distribution of the primary disease process in 129 patients*

Benign ($n=81$)	Patients	Malignant (($n=48$)	Patients
Gallstone disease	73 (56·6)	Carcinoma pancreas	25 (19·4)
Biliary stricture	4 (3·1)	Carcinoma ampulla	6 (4·7)
Acute pancreatitis	2 (1·6)	Carcinoma bile ducts	10 (7·8)
Chronic pancreatitis	2 (1·6)	Carcinoma gallbladder	4 (3·1)
		Secondary carcinoma	3 (2·3)

Values in parentheses are percentages

Table 2 *Principal operative procedure in 129 patients*

	Primary pathology	
Operation	Benign	Malignant
All exploration of common bile duct	76	4
Exploration of common bile duct alone	51	1
All biliary–enteric anastomoses	26	46
Choledochoduodenostomy (side-to-side)	23	8
Choledocho- or hepaticojejunostomy (Roux-en-Y)	3	21
Pancreaticoduodenectomy	—	12
Excision of ampulla	—	5
Other	4	1

Operative management

All operations were performed by a consultant or senior registrar. A prophylactic antibiotic regimen, based on tetracycline lavage supplemented with 500 mg tetracycline intravenously on induction of anaesthesia, was followed[10]. After induction of anaesthesia 20 g of mannitol was given intravenously. Bile culture was routine. Primary closure without T-tube drainage was routine after exploration of the common bile duct. All biliary–enteric anastomoses were made with a single layer of continuous monofilament suture The operations performed are shown in *Table 2*.

Postoperative management

Patients were catheterized and hourly urine volumes were measured Intervention occurred when the volume in two consecutive hours was less than 20 ml/h. In the event of oliguria, the policy was to give a volume load of colloid/crystalloid solution, either plasma protein solution or dextran 70 If oliguria persisted after fluid loading intravenous mannitol or low dose dopamine infusion, or both, were administered. Other diuretics were avoided.

Results

Infected bile was present in 58 (71·6 per cent) patients with benign disease and in 15 (31·3 per cent) patients with malignant disease. Infected bile was not related to the serum level of bilirubin. The bilirubin level was significantly higher in patients with malignant disease (mean ± 1 s.d., 237 ± 131 μmol/l) compared with those with benign disease (109 ± 102 μmol/l; $P<0{\cdot}0001$, Student's t test).

Postoperative mortality

Six (4·7 per cent) patients died. Four of the deaths occurred in the 38 patients with a pre-operative bilirubin level >200 μmol/l (mortality 10·5 per cent) with 2 deaths in the 22 patients with a bilirubin >300 μmol/l (mortality 9·1 per cent). The differences between groups were not statistically significant Three women and three men with a mean age of 76 years (range, 66–82) died. Two patients had benign disease and four had malignant disease. The duration of jaundice was <1 month in all fatal cases. Significant intra- or postoperative haemorrhage occurred in five of these six patients.

Case reports

Case 1. A 66-year-old man suffered a cardiorespiratory arrest immediately after uncomplicated pancreaticoduodenectomy. He sustained irreversible brain damage and died 2 weeks later.

Case 2. A 73-year-old obese woman underwent pancreaticoduodenectomy for a 1·5 cm carcinoma in the head of the pancreas. The decision against a palliative bypass was influenced by the small size of the tumour; she died 18 days postoperatively (despite a second laparotomy) as a result of leakage from the pancreatic anastomosis.

Case 3. A 77-year-old diabetic man with advanced carcinoma of the pancreas and a chronic gastric ulcer who had a palliative bypass procedure and vagotomy and gastro-enterostomy, died on the seventh postoperative day of haemorrhage from gastric erosions which were confirmed at autopsy.

Case 4. A 79-year-old man with acute-on-chronic cholecystitis, choledocholithiasis, portal hypertension, pre-operative septicaemia, renal failure and severe liver dysfunction (serum bilirubin 552 μmol/l) which progressed postoperatively died after cholecystectomy and exploration of the common bile duct which was associated with profound haemorrhage.

Case 5. An 82-year-old woman died of renal failure. Conservative management of acute cholecystitis with choledocholithiasis and cholangitis was unsuccessful. At cholecystectomy she suffered iatrogenic injury to the common bile duct which was repaired immediately. Mismanagement was evidenced by failure to follow stated guidelines on monitoring postoperative urine flow. Corrective measures, which were instituted too late, precipitated left ventricular failure

Case 6. A 79-year-old woman underwent cholecystectomy and hepaticojejunostomy for locally advanced carcinoma of the gallbladder. In all, 5 units of blood were transfused peroperatively and a further 4 units of blood during the first postoperative day. She died suddenly on the second day. Autopsy confirmed extensive residual malignant disease and intraperitoneal haemorrhage.

Postoperative morbidity

The distribution of postoperative morbidity is shown in *Table 3*.

Wound infection. One wound infection occurred in hospital and three after discharge from hospital giving a total of four (3·1 per cent). There was no significant difference between the incidence of wound infection in patients with non-infected bile (3 out of 48, 6·3 per cent) compared with those with infected bile (1 out of 73, 1·4 per cent). Results of bile culture were not available in eight patients, none of whom developed wound sepsis.

Septicaemia: A total of 11 (8·5 per cent) patients received pre-operative therapeutic antibiotics for septicaemia secondary to biliary or pancreatic sepsis, 2 of whom had evidence of postoperative septicaemia. Clinical postoperative septicaemic

Table 3 *Postoperative morbidity in 129 patients*

Complication	n	%
Pneumonia	12	9·3
Septicaemia	2	1·6
Wound infection:		
In hospital	1	0·8
Late	3	2·3
Total	4	3·1
Intraperitoneal sepsis	5	3·9
Central venous catheter sepsis	2	1·6
Delayed gastric emptying	1	0·8
Subacute colonic obstruction	2	1·6
Intra-operative haemorrhage	13	10·1
Postoperative haemorrhage	4	3·1
Renal dysfunction	6	4·7

episodes, treated with systemic antibiotics but without confirmatory blood culture, occurred in a further three patients, one of whom died (the 73-year-old woman with postoperative sepsis after pancreaticoduodenectomy). Coliform organisms accounted for all the episodes in the 11 patients with a positive blood culture and in 6 a similar organism was present in the bile.

Peritoneal infection. Three (2·3 per cent) of the five (3·9 per cent) patients developing intraperitoneal sepsis did so after pancreaticoduodenectomy. In two this was related to leakage from the pancreatic anastomosis and in the third infected ascitic fluid was drained percutaneously. The other two patients developed a biliary–cutaneous fistula after choledochojejunostomy to bypass pancreatic cancer in one and recurrent gastric carcinoma in the other. These were successfully managed conservatively and the patients were discharged on the 12th and 25th postoperative days, respectively.

Postoperative renal function. Of the 129 patients 60 (46·5 per cent) showed a rise in postoperative serum creatinine (range, 1–172 μmol/l). A fall in postoperative creatinine occurred in 52 (40·3 per cent) patients and there was no change in serum creatinine in 17 (13·2 per cent) patients. There was no association between the level of bilirubin and a rise in creatinine after operation.

Seventeen patients had pre-operative renal impairment (serum creatinine >130 μmol/l) but only one of these patients subsequently developed renal dysfunction. Renal dysfunction occurred in six (4·7 per cent) patients of whom five had infected bile and three had a serum bilirubin in excess of 300 μmol/l. Of the 22 patients with a serum bilirubin >300 μmol/l 3 (13·6 per cent) developed renal dysfunction compared with 3 of 107 (2·8 per cent) patients with a bilirubin <300 μmol/l, but this difference was not statistically significant. Two patients with perioperative septicaemia developed renal dysfunction: one had suppurative cholangitis and multiple micro-abscesses in the liver pre-operatively and the second was associated with leakage from pancreaticojejunal anastomosis.

Three of the six patients with renal dysfunction died although renal failure was a definite factor in only one. The commonest measure used to restore adequate hourly urine flow postoperatively was colloid infusion in 40 patients. In addition, ten patients were given mannitol and three dopamine. These measures were effective in terms of preventing renal failure in all cases except the 82-year-old woman who died. No patient was treated with haemodialysis.

Other complications. A total of 13 (10·1 per cent) patients had intra-operative bleeding requiring transfusion of two or more units of blood, four of whom subsequently died. A further four (3·1 per cent) patients, one of whom died, had postoperative bleeding requiring transfusion of 2, 2, 3 and 6 units of blood, respectively.

Discussion

The reported mortality in surgical relief of obstructive jaundice varies greatly (4–43 per cent) and the higher rates, particularly in malignant disease, have been quoted to support the use of pre-operative drainage or non-operative intervention[2]. Multivariate analysis has shown three important pre-operative risk factors: bilirubin >200 μmol/l, malignancy, and a haematocrit <30 per cent[5]. In the present series the mortality rate was 4·7 per cent overall and increased to 10·5 per cent when the serum bilirubin level was >200 μmol/l.

High mortality rates are to be expected in advanced malignancy with metastatic disease[2,11]. In our series 37·2 per cent of patients had malignancy and the mortality was higher in patients with malignant disease, although not significantly so (benign 2·5 per cent *versus* malignant 8·3 per cent, $P>0{\cdot}25$, Fisher's exact test). The ratio of malignant to benign disease is lower than in many series but is comparable with other Scottish reports[12]. Our low overall mortality may be partly attributable to the relatively high proportions of patients with benign disease and with a bilirubin <200 μmol/l. The haematocrit was >30 per cent in all the patients who died. Significant intra- or postoperative haemorrhage occurred in five of the six patients who died, but haemorrhage was directly responsible for only two deaths.

Pre-operative decompression of the biliary tree by percutaneous or endoscopically placed prostheses has been advocated, to reduce postoperative morbidity and mortality[1,2,7,8], but is associated with important and possibly unacceptable morbidity Biliary decompression may not reduce operative risk or mortality and prolongs hospital stay[5,6,9,13,14]. In our experience the mortality in patients with a serum bilirubin in excess of 200 μmol/l compares favourably with most series in which pre-operative decompression was used[1,2,7,9].

Two of the six deaths (cases 2 and 5) resulted from faulty judgement or technique and were possibly avoidable. In addition, two patients (cases 4 and 6) would now be appropriately considered for non-surgical biliary drainage because of the high operative risks.

Postoperative infective complications in jaundiced patients are common despite the apparently optimal use of antibiotics[6,15]. In this series postoperative septicaemia occurred in 1·6 per cent (or 3·9 per cent if the patients without confirmatory bacteriology are included) of patients, wound infection in 3·1 per cent and intraperitoneal infection in 3·9 per cent. Postoperative septicaemia was related to serious intrahepatic or pancreatic sepsis in three patients. Peroperative choledochoscopy was probably responsible in the fourth. The fifth patient who had pre-operative septicaemia with coliform organisms treated with an appropriate cephalosporin was given the same agent postoperatively because of clinical septicaemia (although blood cultures were negative). Three of the four wound infections occurred in patients with sterile bile and all three presented late, after the patient had left hospital. The responsible organisms are unknown. *Escherichia coli* and an enterococcus were cultured from the wound of the fourth patient who developed a wound infection in hospital and also had *E. coli* in the bile.

The antibiotic regimen, based on peroperative tetracycline lavage and a single intravenous dose of the same agent, appeared effective in preventing both wound and systemic sepsis despite the fact that only approximately 70 per cent of the organisms cultured in bile were sensitive to tetracycline on conventional sensitivity testing.

Intraperitoneal infection was related to anastomotic leakage rather than operative contamination by infected bile.

Impaired wound healing in obstructive jaundice is influenced by factors such as malignancy and malnourishment rather than obstructive jaundice *per se*, and may be responsible for an increased frequency of wound dehiscence (2–4 per cent)[16]. Wound dehiscence did not occur in this series in which a midline incision with mass closure was routine.

In relation to operation, glomerular filtration rate decreases in 65–75 per cent of patients with obstructive jaundice[4,17,18], and postoperative renal insufficiency or frank acute renal failure still affects nearly 20 per cent of patients[4,13]. A postoperative rise in serum creatinine was observed in 46·5 per cent of patients in the present series and 31 per cent of patients required active measures to promote urine flow. Renal dysfunction as defined occurred in only 4·7 per cent of patients which is similar to the 8 per cent incidence in comparable patients in whom the same definition of renal dysfunction was used[6].

Among various factors implicated in the genesis of renal failure in jaundiced patients current interest focuses on gut derived endotoxins[19]. Circulating endotoxin activates a variety of intravascular responses which induce renal vasoconstriction, redistribution of intrarenal blood flow[20], and glomerular fibrin deposition[21]. In hepatobiliary disease the clearance of endotoxins, normally denied systemic access by the liver reticulo-endothelial system, is depressed as a result of overloading[22]. After surgery endotoxin may be demonstrated in the peripheral blood in at least 50 per cent of patients with jaundice[17–18] and concomitant renal impairment is common. In contrast, renal impairment is rare in the absence of endotoxaemia[17,19].

Several measures have been used to reduce or abolish endotoxaemia including whole gut irrigation and administration of pre-operative antibiotics, oral bile salts, and lactulose[23]. There is evidence that pre-operative oral bile salts, in particular sodium deoxycholate, may prevent postoperative renal failure in jaundiced patients[18]. Before 1983, when oral sodium deoxycholate was not used, four (5·1 per cent) patients developed renal dysfunction. Since the introduction of bile salts in 1983 two (4 per cent) patients have developed renal dysfunction. We are clearly unable to draw any conclusion on the value of deoxycholate.

Although ursodeoxycholic acid also reduces portal endotoxaemia during operation it appears not to affect systemic endotoxaemia and its use has not been associated with a significant difference in postoperative morbidity or mortality[24].

Lactulose also has been shown to reduce the incidence of endotoxaemia in the operative portal and postoperative systemic blood, and has prevented a fall in postoperative renal function in patients[25]. Its potential to prevent postoperative renal failure in jaundiced patients has yet to be fully evaluated.

A recent study has emphasized the critical role of postoperative sepsis in the development of renal dysfunction in jaundiced patients[26], and the low incidence of peritoneal sepsis in this study is probably a major contributory factor to the relative infrequency of serious renal impairment. In our experience perioperative septicaemia, perhaps surprisingly, was not a particular risk factor for renal dysfunction. Two of the fourteen patients developed renal dysfunction but one had serious intraperitoneal sepsis.

In our clinical practice, we cannot envisage improvement in mortality or morbidity as a result of introducing the complexity of routine or almost routine pre-operative drainage or intubation of the biliary tract. The attendant hazards and resulting delay in definitive surgical treatment are definite disadvantages, aside from the lack of evidence of benefit. These reservations may not apply to the relief of jaundice by endoscopic sphincterotomy in the occasional patient in whom the risks of operation are clearly very high. In these circumstances the procedure would be considered a definitive alternative rather than a preparatory step in management.

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Pancreaticogastrostomy: the preferred operation for pain relief in chronic pancreatitis

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We present the results of surgery in 53 patients with intractable pain due to chronic pancreatitis associated with pancreatic duct dilatation. Using a limited mucosal to mucosal anastomosis over a silastic T tube the main pancreatic duct was drained in 33 patients into a Roux-en-Y jejunal loop (pancreaticojejunostomy, PJ) and in 20 patients into the stomach (pancreaticogastrostomy, PG). There was one postoperative death in the PJ group and none in the PG group. All patients were followed up for a minimum of four years. There was significantly greater pain relief in the PG group both at 1 ($P<0{\cdot}01$) and 4 years ($P<0{\cdot}05$) after surgery. We argue that PG is the operation of choice to relieve intractable pain in most patients with chronic pancreatitis associated with duct dilatation.

Keywords: Chronic pancreatitis

The indications for surgery and the correct operation for chronic pancreatitis is a contentious subject. The main indication is intractable pain[1–3], and operations for this broadly fall into three types—resection of part or all of the gland, duct drainage and denervation. The best results have been obtained in those patients with pancreatic duct dilatation who undergo a drainage procedure[4–6].

In this surgical unit we have drained a short segment of the dilated pancreatic duct either into a Roux-en-Y jejunal loop or the stomach using mucosal to mucosal apposition over a silastic T tube. We have studied the results of these procedures when used in 53 patients over a 12-year period.

Patients and methods

Between 1972 and 1983, 33 patients underwent pancreaticojejunostomy (PJ) and 20 patients underwent pancreaticogastrostomy (PG) for pancreatic duct obstruction due to chronic pancreatitis Patients underwent PJ or PG when there were localized or short segment main pancreatic duct obstructions due to strictures or calculi. During this 12-year period another four patients had duct dilatation due to extensive stricturing throughout the length of the main pancreatic duct and were treated with longitudinal pancreaticojejunostomies. These four cases are not considered further.

Pre-operative details of patients are shown in *Table 1*. The indication for surgery in all patients was intractable pain, and all had dilatation (> 5 mm) of the main pancreatic duct at operation. The choice between PJ and PG was not based on any specific factor, however early in the series PJ was performed in most patients, but as the results of PG became apparent this became the commoner operation. Fourteen (42 per cent) PJ patients and seven (35 per cent) PG patients had undergone previous surgery for chronic pancreatitis (sphincteroplasty, bile duct drainage, cyst drainage, pancreatic duct drainage or distal pancreatectomy). Patients operated on in the early part of the series had pancreatic duct dilatation diagnosed by intra-operative pancreatography, but in the latter part of the series a pre-operative diagnosis was usually made by ultrasound, CT scan or endoscopic retrograde cholangiopancreatography (ERCP). As well as PJ or PG three patients also underwent a bile duct drainage procedure, and one patient underwent a Polya gastrectomy

The methods of PJ and PG used have been described previously[7,8]. The anterior surface of the pancreas is approached via the gastrocolic omentum. The dilated part of the pancreatic duct is found by palpation and with reference to the pre-operative ERCP or scans. A short incision is made through the pancreatic parenchyma to open the duct Stay sutures are inserted and the duct is probed both distally and proximally Any strictures are dilated and as many calculi as possible removed. A peroperative pancreaticogram is performed through a silastic T tube. The pancreatic duct is then sutured to a Roux-en-Y jejunal loop (PJ) or to the posterior wall of the stomach (PG) using a mucosa to mucosa technique[8]. The long end of the T tube is brought out to the exterior via the Roux loop or via the anterior gastric wall. The T tube is removed between 1 and 2 months after the operation following a T tube pancreaticogram.

Patients have been graded at 1, 4 and 8 years after surgery as follows· 'good'—pain free or only minor discomfort which does not interfere with everyday activities; 'fair'—episodic pain requiring analgesia, but not requiring hospital admission; and 'poor'—severe pain requiring regular analgesia, or hospital admission, or further surgery.

Comparisons of the numbers of patients graded as 'good' at follow-up were made with the χ^2 test and Yates' correction where necessary.

Results

Calculi were removed from the pancreatic ducts of 16 patients (48 per cent) undergoing PJ and six patients (30 per cent) undergoing PG. Chronic pancreatitis was confirmed by histology in all patients. Median blood loss in patients undergoing PJ alone was 321 ml and PG alone was 273 ml.

There was one postoperative death (within 30 days) in the PJ group (due to a small bowel fistula), and no deaths in the PG group. In the PJ group one patient developed an anastomotic leak and another a burst abdomen, and in the PG group one patient had a pancreatic abscess and another an intraperitoneal bleed following surgery. Three deaths have subsequently occurred in the PJ group—cerebrovascular accident (at 2 years after operation) and chronic pancreatitis in two patients (at 7 and 9 years). One patient in the PG group died from breast carcinomatosis within 1 year of surgery.

All patients who have survived and not undergone reoperation have been followed up for a minimum of 4 years (PJ mean = 9·7 years, PG mean = 6·5 years). One patient in the PJ group was lost to follow-up 4 years after surgery. The results at

Table 1 *Pre-operative details of both groups of patients*

	Pancreatico-jejunostomy PJ *n*=33	Pancreatico-gastrostomy PG *n*=20
Sex (male.female)	25:8	15:5
Age range (median)	34–69 (41)	23–55 (46)
Cause	22 (67%)	14 (70%)
Alcohol	8	5
Idiopathic	2	0
Pancreas divisum	1	0
Gallstones	0	1
Trauma		
Narcotic dependence	5	4
Diabetes	2	2
Steatorrhoea	3	2
Previous pancreatic surgery	11*	7
	3†	2

* One previous operation, † two previous operations

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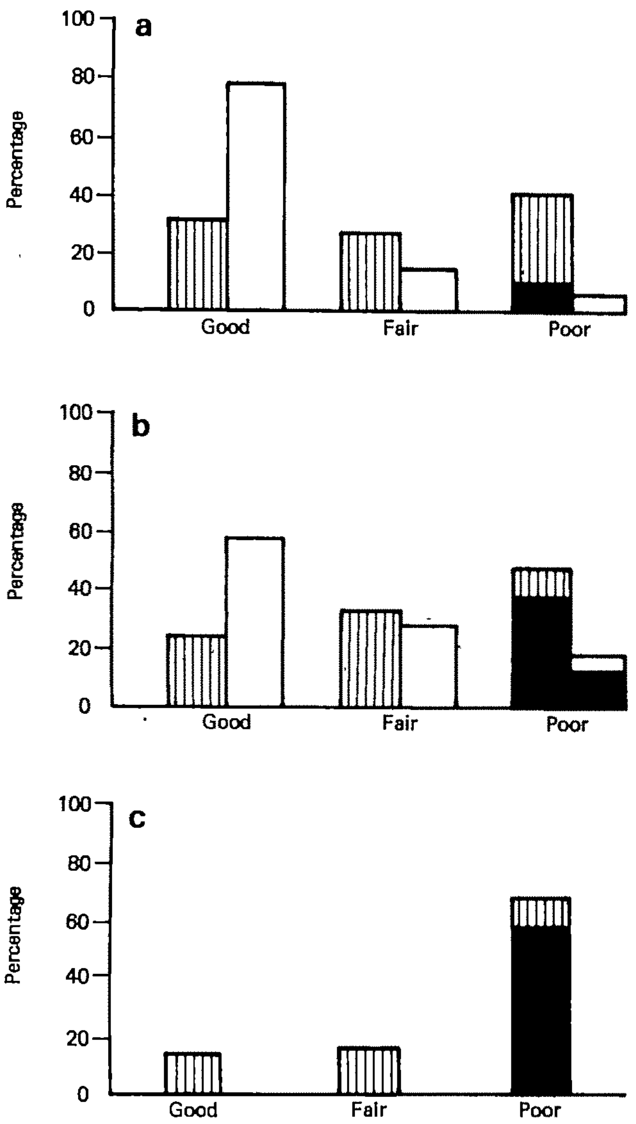

Figure 1 *Follow-up results of patients graded at 1, 4 and 8 years.* □, *Pancreaticogastrostomy (PG),* ▥, *pancreaticojejunostomy (PJ),* ■, *further surgery.* **a**, *At 1 year (PG,* n = *19, PJ,* n = *32),* **b**, *at 4 years (PG,* n = *19, PJ,* n = *31),* **c**, *at 8 years (PJ,* n = *27). The 8 year results of PG are in the text*

1, 4 and 8 years after surgery are shown in *Figure 1*. Only eight of the patients in the PG group have been followed up for 8 years and so this group has not been included in *Figure 1*. However at 8 years the results in five (62 per cent) of these patients have been graded as good, two as fair and one as poor. There were significantly more patients graded as good in the PG group at 1 year ($\chi^2 = 7{\cdot}37$, d.f. = 1, $P < 0{\cdot}01$) and 4 years ($\chi^2 = 4{\cdot}93$, d.f. = 1, $P < 0{\cdot}05$) after surgery compared with the PJ group. Postoperative alcohol consumption was admitted by 12 (37 per cent) PJ patients and 6 (30 per cent) PG patients. Postoperative narcotic abuse has occurred in six PJ patients and two PG patients. In patients without pre-operative pancreatic exocrine or endocrine insufficiency diabetes has developed in two PJ patients and one PG patient. Postoperative steatorrhoea has developed in six PJ and six PG patients. Including those with pre-operative steatorrhoea 40 per cent of PG and 28 per cent of PJ patients now have steatorrhoea. Within 4 years of operation further surgery for chronic pancreatitis has been necessary in 11 PJ patients (PJ, four patients; PG, two patients; distal pancreatectomy, two patients; laparotomy, two patients; choledochoduodenostomy, one patient) and in two PG patients (PJ, distal pancreatectomy).

Discussion

Comparisons of operations for chronic pancreatitis are made difficult because the procedures are performed at different stages of a disease with an unpredictable natural history. Alcohol is the commonest cause of chronic pancreatitis, and abstention is probably the greatest single contributory factor to the results of surgery[9] In this series blood alcohol levels were not routinely performed at follow-up, but at least 30 per cent of patients admitted to alcohol consumption after surgery.

Of the various operations that have been described to relieve pain in chronic pancreatitis the best results are obtained in patients who have dilated pancreatic ducts and undergo duct drainage[5,6]. Although partial pancreatic resection may be indicated in the few patients with pancreatitis localized to one part of the gland we avoid total pancreatectomy because of the higher operative mortality and the subsequent exocrine and endocrine insufficiency. A fatal insulin overdose is not uncommon in narcotic or alcohol dependent diabetics.

In 50–75 per cent of patients with chronic pancreatitis duct dilatation is present[1,2,9,10], and it is in these patients that a duct drainage procedure may be indicated. PJ was first proposed by Coffey in 1909[11], and 2 years later Link[12] reported pancreatostomy for removal of pancreatic duct calculi. Ductal drainage was described in 1954 by DuVal[13] and Zollinger *et al.*[14] who advocated excision of the pancreatic tail and the formation of a caudal PJ. Subsequently Puestow and Gillesby[15] introduced longitudinal PJ, but this necessitated resection of the tail of the pancreas. This operation was later refined by Partington and Rochelle[16] making resection unnecessary. Since then results of longitudinal PJ have been extensively reported and pain reduction has been claimed to occur in 56–94 per cent of patients[2,5,17–19]. However, selection of patients, length of follow-up and methods to assess results vary greatly between studies.

In our experience pancreatic duct obstruction is usually due to one or two isolated strictures often with associated ductal calculi. Although the main pancreatic duct is often tortuous, true septation ('chain-of-lakes') is rarely seen[20]. Except in patients with extensive stricturing throughout the pancreatic duct we have avoided longitudinal PJ and instead have used a limited mucosal to mucosal pancreatico-enteric anastomosis formed over a silastic T tube Early in our series we more commonly performed a PJ anastomosis, but those patients who underwent a PG anastomosis appeared to progress better after surgery. The results of this study support this view and PG has now become our standard operation for patients with pancreatic duct dilatation and intractable pain. Greater pain relief was obtained in the PG group 1 year ($P < 0{\cdot}01$) and 4 years ($P < 0{\cdot}05$) after surgery. Within 4 years of operation 35 per cent of PJ patients had undergone further surgery for chronic pancreatitis but this was required in only 10 per cent of PG patients PG has a low morbidity and mortality, causes little blood loss, is minimally destructive to the gland and does little to hinder any further surgery that may be required for chronic pancreatitis. Care, however, must be taken in performing a precise mucosal to mucosal anastomosis around the T tube. PG was first described by Tripodi and Sherwin in 1934[21], and has since been advocated for duct drainage after partial pancreatic resection[15,22–26]. In order to maintain a patent anastomosis Telford *et al.*[25,27] have stressed the importance of performing a pancreatic duct to gastric mucosa anastomosis. We are only aware of one previous study[28] reporting the results of PG in chronic pancreatitis.

Following duct drainage some patients have continued evidence of loss of pancreatic function as measured by the development of insulin-dependent diabetes or steatorrhoea[2,17,29], and this has been attributed to the continuing destructive disease rather than due to the surgery[9,20]. Overall 40 per cent of PG patients and 28 per cent of PJ patients have steatorrhoea. The higher prevalence in the PG group may be due to the inactivating effect of gastric acid on the pancreatic enzymes.

Elevated intraductal pressure is associated with dilated pancreatic ducts[30] and causes pain[29–31]. The rationale of pancreatic duct drainage is to reduce the pressure, and thereby reduce the pain. An additional benefit is to drain the exocrine secretions from obstructed ducts into the intestines. There is no evidence for ductal hypertension in patients with normal sized ducts[1], and duct drainage procedures fail to provide pain relief in such patients[32]. However the pathophysiology of ductal dilatation and the benefits of duct drainage have been questioned, since similar ductal changes are present at ERCP in patients with chronic pancreatitis who do and do not have pain[33], and Holmberg *et al.*[9] found that only 25 per cent of caudal and 57 per cent of longitudinal PJ remained patent and patency was not correlated with better pain relief. This has led some[5] to suggest that an early good result following duct drainage may be a placebo effect, and that a late good result may actually reflect the natural history of the disease (i.e. natural 'burnout' of chronic pancreatitis). This theory is not supported by the results of our study since different outcomes followed two different drainage procedures. Stenosis of the PJ or PG was invariably found by ERCP or at laparotomy in those patients who developed recurrent pain, whereas patients with minimal symptoms or abdominal pain unrelated to the pancreas usually had patent anastomoses present at postoperative ERCP. It seems that the better results from PG may relate to the greater long-term patency of the anastomosis. A possible reason why a PG may be less likely to stenose could be due to the lack of activation of the pancreatic enzymes at the site of the anastomosis because of the low pH and absence of jejunal enzymes. However these factors may also be responsible for the higher incidence of steatorrhoea present in the PG group.

The results of this study show that PG is an effective operation for chronic pancreatitis. The results of PG are similar to the published results of longitudinal PJ, and since no Roux-en-Y has to be constructed PG is a quicker procedure, and one that causes minimal anatomical disruption. We advocate that this is the surgical treatment of choice for most patients with intractable pain due to duct dilatation. Longitudinal PJ may still have a role in those patients who have extensive stricturing throughout the length of the pancreatic duct.

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Contact laser or conventional cholecystectomy: a controlled trial

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There have been claims that the use of lasers in surgery is associated with reduced operative blood loss, trauma, postoperative pain and improved postoperative mobility. With the development of sapphire probes capable of transmitting neodymium yttrium aluminium garnet (Nd:YAG) laser light, it is now feasible to perform direct-contact low-power laser surgery. In a small randomized controlled trial, we have compared cholecystectomy performed by conventional methods (n = 11) with the same operation performed by contact laser (n = 10). Operative time, blood loss, operative stability, analgesic requirement, mobility and response to the trauma of surgery were compared. The only differences between the two groups were a significantly increased wound infection rate (P = 0·051) in the laser surgery group and a significantly increased length of operating time (P = 0·001). Thus, the laser did not confer any advantage over conventional surgery.

Keywords: Low power, contact laser, surgical trauma

Since the first development of a laser in 1960[1] there has been great interest in the application of lasers in medicine. The attractions are of a regulated, controlled beam of light energy that can be precisely applied. One disadvantage has been the means of applying laser light to patients. The carbon dioxide (CO_2) laser (wavelength 10062 nm) has to be applied by an articulated arm attached to the laser generator and is a non-contact method of application. The properties of the CO_2 laser include tissue division in a manner similar to a scalpel and it has been called the 'light knife'[2]. The neodymium yttrium aluminium garnet (Nd:YAG) laser (wavelength 1064 nm) has properties of greater tissue penetration and coagulation than the CO_2 laser. It has been used to treat bleeding peptic ulcers and to recanalize oesophageal and rectal tumours[3,4]. Nd:YAG laser light can be transmitted via flexible quartz fibres, a delivery system that is easier to use than the articulated arm of a CO_2 laser.

The tissue penetration of the Nd:YAG laser, whilst applicable at appropriate powers, causes thermal tissue damage up to 5 mm when used at high powers (50–100 W)[5]; this is too great and imprecise to be of use as a thermal knife. A further disadvantage of the use of laser light in general surgery is the non-contact method of application, the sense of touch being essential in general abdominal surgery. The development of artificial sapphire probes[6] into which Nd:YAG laser light is passed allows direct contact laser surgery at low powers (15–20 W) to be performed.

There have been claims that the use of lasers (both non-contact and contact) in surgery is associated with improved wound healing, reduced wound infection, reduced postoperative pain and increased postoperative mobility, as well as reduced operative blood loss[7–10]. With the development of a practical system for the use of Nd:YAG energy in general surgery, we have carried out a randomized controlled trial to assess the possible use of low-power contact Nd:YAG laser in operative surgery.

Materials and methods

The laser used was a Pilkington Medical Systems Fiberlase 100 Nd:YAG laser (This, when purchased, cost £36000.) Laser light was transmitted via a quartz fibre which was fed into a metal handpiece at the end of which was attached an artificial sapphire probe (Surgical Laser Technology, Keighley, W. Yorkshire). The patient and all theatre personnel wear protective eye goggles Laser procedures were carried out in accordance with DHSS guidelines[11].

Twenty-one patients admitted for routine cholecystectomy were studied. The nature of the study was explained to the patients and informed consent was obtained. The study was approved by the Hospital Ethical Committee. All patients were allocated, at random, into two groups. group 1 (control) to undergo surgery with knife and diathermy and group 2 to be operated on using the contact laser probe throughout the operation. All patients had normal liver function tests, no history of jaundice and none had had an episode of acute cholecystitis for at least 4 months. The two groups were equally matched with regard to past medical history, female:male ratio and age Group 1 consisted of 11 patients (9 women and 2 men) with a mean age (±s.d.) of 50·4 ± 16·8 years and a mean weight (±s.d.) of 72 ± 20·3 kg. Group 2 consisted of 10 patients (8 women and 2 men) with a mean age (±s.d.) of 54·5 ± 16·5 years, and a mean weight (±s.d.) of 67 ± 8·4 kg

Pre-operative fitness was assessed on the American Society of Anaesthetists' grading. In this, Grade 1 = a normal, healthy patient, Grade 2 = a patient with mild systemic disease, Grade 3 = a patient with severe systemic disease that is not incapacitating, Grade 4 = a patient with an incapacitating systemic disease that is a constant threat to life and Grade 5 = a moribund patient who is not expected to survive 24 h with or without operation[12]. The median grade in both groups was two.

The metabolic response to surgery was assessed by measuring glucose, creatinine phosphokinase (CPK) and cortisol pre-operatively and at 12, 24 and 36 h postoperatively Urine was collected for 24 h pre-operatively and for two successive periods of 24 h postoperatively and successive potassium, phosphate, calcium, sodium and nitrogen excretion were measured. The following were measured pre-operatively and at 24 h postoperatively: Hb, WBC, PCV, sodium, potassium, urea, creatinine and liver function tests

Operative details

Patients in both groups received lorazepam 2 mg orally 2 h before surgery. Anaesthesia was induced in all patients with thiopentone (3·5–5·0 mg/kg), the trachea was intubated with the aid of alcuronium and

Table 1 *Operative details*

Operative parameters	Control (*n* = 11)	Laser surgery (*n* = 10)	*P*
Blood loss (ml)	95 ± 75	146 ± 107	n.s.
Incision time (min)	3·0 ± 1·0	9·3 ± 3·3	0·001
Operative time (min)	29·9 ± 10·3	57·5 ± 12·9	0·001
Operative minus incision time (min)	26·9 ± 10·7	48·7 ± 13·5	0·001
Anaesthetic supplementation	7/11	7/10	n.s

n.s., not significant. Values are means ± s.d.

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fentanyl given as a bolus for analgesia (200–250 $\mu g\,kg^{-1}$). The lungs were ventilated with 75 per cent nitrous oxide in oxygen. Anaesthesia was supplemented, if required, with either fentanyl (100 μg) or the addition of halothane 0·5 per cent to the inspired gas mixture. All operations were performed by the same surgeon and anaesthetist.

All patients underwent an initial laparotomy followed by intra-operative cholangiography and cholecystectomy. There were no explorations of the common bile duct. Group 1 (control) underwent surgery using a steel knife and diathermy (Diodon 400, Downs Surgical). In group 2 the contact laser probe was used in place of knife and diathermy throughout the procedure.

Sodium chloride (150 mmol/l) was administered intravenously at a rate of 6 $ml\,kg^{-1}\,h^{-1}$ during surgery and at 2 $ml\,kg^{-1}\,h^{-1}$ postoperatively for 24 h. Blood transfusion was not required in any of the patients. Postoperative analgesia was provided with papaveretum (15–20 mg IM) on demand.

During operation the following were measured: incision time, total operative time, operative minus incision time, anaesthetic supplementation, blood loss (measured by weighing dry swabs), numbers of swabs and instruments used. Heart rate and mean arterial pressure were recorded using a Dinamap vital sign recorder (Criticon).

Postoperatively, both narcotic analgesic requirement and oral analgesia (paracetamol 1 g as required) were recorded as was time of request for narcotic analgesia from the end of operation. Pain was recorded using a visual linear analogue scale. The following were also recorded: major complications, wound infections, minor wound problems, days in hospital and time to mobilization.

Results were expressed as means and standard deviations (s d.) and statistical comparisons were analysed where appropriate by Student's t test and Fisher's two-tailed exact probability test. P values of less than 0·05 were considered to be significant.

Results

Operative details are given in *Table 1* and postoperative recordings in *Table 2*. Incision, total operative time and operative time minus incision time were significantly slower in the laser surgery group ($P = 0·001$). The number of wound infections in the laser surgery group was just significant ($P = 0·051$) compared with the control group.

Table 2 *Postoperative details*

Postoperative parameters (mean ± s.d.)	Control ($n = 11$)	Laser surgery ($n = 10$)	P
Number of narcotic analgesic injections required	3 ± 1	3 ± 1	n s.
Number of times oral analgesic required	12 ± 8	12 ± 6	n s.
Days to reach zero pain	7 4 ± 3·1	6·3 ± 1·5	n.s
Days in hospital	9·8 ± 4·0	13·0 ± 5·8	n s.
Serious complications	0/11	2/10	n.s.
Wound infections	1/11	5/10	0.051
Wound problems	2/11	4/10	n.s

n s., not significant Values are means ± s.d.

There was no difference between the two groups with regard to Hb, PCV, liver function tests, electrolytes or measurement of the surgical response to trauma by CPK and cortisol levels and urinary nitrogen, phosphate and potassium excretion. There was no difference in operative stability between the two groups (*Table 3*).

In the control group there were no serious complications. In the laser surgery group there were two complications; a prolonged ileus and a left subphrenic abscess that required formal drainage. The wound infections were documented by positive bacteriology. The wound problems were minor, such as haematoma, delayed healing, eschar formation and failed superficial skin healing.

There was no difference between the two groups in times of mobilization. Analgesic requirement was similar in both groups, all patients requiring at least one injection of papaveratum after operation (group 1, 2·8 ± 1·9 h, group 2, 3·9 ± 1·4 h) reducing to a final fifth dose for two patients in each group, at 36·7 h in group 1 and 44·1 h in group 2. Visual linear analgesic pain scores (mean ± s.d.) on the first postoperative day were 6 ± 2·7 in group 1 and 7·5 ± 2 in group 2 and at 5 days were 1·7 ± 2·3 and 1·3 ± 1·5, respectively. A zero score was reached at 7·4 ± 3 days in group 1 and 6·3 ± 1·5 days in group 2.

Discussion

For any new system to replace the use of knife and diathermy in surgical practice, clear advantages have to be shown. In this study the use of contact laser was associated with significantly longer incision and operating times than was the use of a knife. This was because the probe cuts only when hot and the cutting rate was slower than when using a knife. Blood loss, perhaps surprisingly in view of the theoretical advantage of small vessel coagulation, was not reduced in the laser group. It may be that such vessels, initially sealed, reopen and bleed and this could perhaps explain the left subphrenic abscess. The prolonged ileus may be the result of increased operative time. The wound problems were those associated with a thermal skin burn, poor skin healing, wide scarring and overall slower wound healing. Biopsies taken at operation confirm that the tissue reaction was as to a burn, with a width of up to 1·0 mm. The laser-made wounds took on average 4 days longer to heal than the knife wounds and a marked fibrinous plaque which developed into an eschar that separated at 7–10 days was seen in all cases where there were wound problems. The difference in wound infections

Table 3 *Operative arterial pressure and heart rate*

	Measured parameters (mean ± s.d.)			
	Mean arterial blood pressure (mmHg)		Heart rate (beats/min)	
Sample recordings at 5 min intervals	Control ($n = 11$)	Laser surgery ($n = 10$)	Control ($n = 11$)	Laser surgery ($n = 10$)
1	79 ± 17	88 ± 18	80 ± 11	90 ± 25
2	91 ± 17	86 ± 11	77 ± 10	79 ± 21
3	102 ± 24	101 ± 19	80 ± 8	82 ± 18
4	106 ± 20	109 ± 18	85 ± 8	82 ± 19
5	106 ± 14	116 ± 18	83 ± 10	84 ± 16
6	108 ± 13	108 ± 22	82 ± 12	81 ± 19
7	118 ± 14	112 ± 34	82 ± 11	86 ± 15
8	—	112 ± 24	—	71 ± 15
9	—	110 ± 25	—	76 ± 14
10	—	105 ± 21	—	76 ± 13
11	—	108 ± 13	—	75 ± 15
12	—	110 ± 13	—	77 ± 18

was just significant. All wounds were soundly healed at 6 months follow-up.

The reasons why laser surgery might be less traumatic than conventional surgery are not clear. Possibilities are that afferent sympathetic nerve fibres are sealed with a reduced cardiovascular stimulation and a reduced centrally mediated metabolic neuroendocrine response to the stress of surgery or, more simply, reduced blood loss. This has not been shown in this study, with no difference between the two groups in terms of operative cardiovascular stability or the normal metabolic response to surgery. Cholecystectomy, however, is not a particularly traumatic operation, but is a common one. There was a subjective impression that contact laser made the removal of an inflamed gallbladder easier. No measurable advantage has been shown in using low-power contact laser in this trial. There are reports of the use of lasers in performing solid organ surgery (liver and spleen) with an operative impression and some measurement of advantage[13]. However, hepatic and splenic surgery are comparatively uncommon compared with other aspects of general surgery. Centres specializing in such surgery may find a place for low-power contact laser as an instrument to be used at specific times during a procedure. The present state of technological development is not such that it can replace conventional methods. It should not be used on skin, agreeing with previous reports on the use of thermal instruments on skin[14,15].

Studies on wound healing show that no thermal device is an improvement on the steel blade[14] (and indeed if infection is taken into account, worse). There are differences between the thermal knives but if they are shown to be inferior to a steel blade[16], of what relevance is this[17]?

With the advent of any new thermal knife, the possible uses of such instruments are redefined. However, these are all similar—hepatic, splenic, renal surgery and perineal and buccal surgery[15].

One objection to the use of any thermal instrument for continuous simultaneous cutting and coagulation is that unnecessary tissue damage is caused as opposed to the theoretically less traumatic, but more precise, technique of tissue division with vessel ligature or careful coagulation as required. There are areas of surgery (in vascular organs) where immediate surface coagulation to reduce blood loss may be desirable. That previous thermal knives have not been taken up immediately for specific uses and indications throughout general surgery would indicate that the problems associated with their use (e.g. cost, tissue sticking/destruction, complicated machinery) may outweigh any advantages.

What are needed are studies comparing all the various thermal instruments for specific procedures. From this, some ideas of the appropriate applications and the pros and cons of each might emerge and enable the surgeon to take up the relevant technique, or not, on the basis of adequate comparative evidence—something that cannot be done at the moment.

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Blunt injuries of the diaphragm

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Rupture of the diaphragm is a potentially serious complication of blunt trauma which can easily be overlooked at the time of presentation. This review examines the incidence and pathogenesis of the injury and discusses diagnosis and management.

Keywords: Diaphragm, blunt injury

Rupture of the diaphragm following blunt trauma is an uncommon injury which may be difficult to diagnose even if the surgeon maintains a high index of suspicion. Patients managed non-operatively may sustain rupture of the diaphragm which does not become clinically obvious until months or years later, and even in patients undergoing surgery, diaphragmatic tears may not be recognized. Late presentation, and its associated morbidity, can be avoided if the correct diagnosis is made during the acute phase after injury.

Although diaphragmatic rupture following blunt trauma may be difficult to diagnose, direct lacerations of the diaphragm present less difficulty in diagnosis and management and will be considered only briefly. There should be no difficulty if the penetrating injury is explored surgically. Nowadays, however, selected patients are managed conservatively[1,2], which may lead to lacerations of the diaphragm being overlooked. Indeed we have seen such a case, where the patient presented to this hospital with subacute intestinal obstruction secondary to a diaphragmatic hernia 3 months after a stab wound to the left chest. This had been managed conservatively at another hospital. At operation for penetrating injuries of the abdomen or chest a thorough inspection of the diaphragmatic surface should be made. In this way most lacerations of the diaphragm will be detected. Many of these lacerations are not complicated by herniation and are easily missed unless sought specifically[3,4].

In contrast, when a diaphragmatic hernia presents months or years after the causative event, the management is similar whether it is secondary to penetrating or blunt trauma. Incisional hernia of the diaphragm following trans-diaphragmatic surgery forms a special group of iatrogenic penetrating injuries which is well recognized and may also lead to intestinal obstruction years after the initial surgery[5,6].

Although penetrating and blunt diaphragmatic injuries differ in terms of their prognosis, incidence of associated injuries, and management, and while the presentation and management problems vary according to the time of presentation, many reports, including some recent publications[7–12], have not differentiated between these distinct groups. This review aims to clarify the diagnosis and management of blunt injuries of the diaphragm as these generally pose more problems and entail a higher mortality than penetrating wounds.

Aetiology

Blunt injury to the diaphragm usually follows severe crushing injuries to the upper abdomen or chest. In seven series reported since 1980, 252 (93 per cent) of 271 cases were caused by a motor vehicle accident[7,13–18]. Other causes included falls (12 cases, 4 per cent) and industrial accidents causing crush injuries (4 cases, 1 per cent). North American series which include both blunt and penetrating injuries report that blunt trauma accounts for only 10–30 per cent of diaphragmatic ruptures[3,7,12,19,20], whereas in western Europe, where penetrating injuries are less frequent, 80–100 per cent of reported diaphragmatic ruptures are due to blunt trauma[16,17,21,22].

Diaphragmatic rupture occurs in 3–8 per cent of patients suffering blunt trauma to the trunk of sufficient severity to require surgical exploration for visceral injury[7,21]. In one North American trauma centre diaphragmatic rupture was found in 0·8 per cent of 7500 patients admitted to hospital after motor vehicle accidents[18].

All reports note a very high preponderance of young adults aged 15–35 years among those sustaining this injury, reflecting the increased risk in this age group of motor vehicle accidents. Although in one series of 56 children aged less than 10 years who had suffered blunt abdominal trauma (of whom 26 needed laparotomy)[23] none had sustained a ruptured diaphragm, nevertheless this injury can occur in this age group[14–16,24–26].

Associated injuries

Because of the severity of the trauma required to rupture the diaphragm, associated injuries are common. Intracranial haematoma (25–55 per cent), fractures of the pelvis (15–55 per cent), fractures of long bones (45–85 per cent) and injury to upper abdominal viscera are the most frequently associated injuries[13,17,18,24,25]. The most frequently injured abdominal viscus is the spleen which is ruptured in 25–60 per cent of cases, while the colon and stomach will each be damaged in up to 9 per cent of cases[13,18,24–26]. In right-sided injuries the liver and great veins will be injured in between one-third and two-thirds of cases[13,18,25]. Significant intra-abdominal injury requiring repair was found in 83 (51 per cent) of 164 evaluable cases[13,17,24,25,27]

Although one might expect that rib fractures would almost invariably accompany this type of injury, this is not the case. Various authors report an incidence of rib fractures of 25–70 per cent in cases of blunt diaphragmatic rupture[13,14,17,24,25,27], with an overall incidence of rib fracture in 92 (47 per cent) of 195 cases. Associated injuries frequently involve more than one major system (e.g. gastrointestinal, cardiovascular, skeletal), and morbidity and mortality increase markedly when more than two systems are affected[21,24].

Despite the frequent association of other injuries, isolated injuries of the diaphragm can occur. Williams, in Australia[13], found that the ruptured diaphragm was the only major injury in 19 (40 per cent) of 47 patients. Visset *et al.*[17], in France, found that 17 (29 percent) of 58 patients with ruptured diaphragm had no other thoraco-abdominal injury, although some of these patients had bony fractures. McCune *et al.*[25] reported that associated injuries were invariably found in patients diagnosed in the early phase after injury (mean 2·5 associated injuries per patient) whereas, in those in whom a late diagnosis of diaphragmatic rupture was made they found less than one associated major organ injury per patient. Thus the patient with isolated rupture, with no associated injury, appears to be at greater risk of late diagnosis. For this reason, all patients with blunt thoraco-abdominal trauma should have a chest radiograph 3 months postoperatively.

In contrast, most series of diaphragmatic rupture diagnosed in the immediate postinjury phase confirm the almost

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invariable presence of associated injuries, with only one exception in the 110 cases reported in four evaluable series[18,21,24,27].

The contribution of a diaphragmatic injury to post-traumatic morbidity is usually minimal, and death, when it occurs, results from other major injuries[13,17,18,21,24]. However, Brooks describes one case in which death resulted from respiratory embarrassment secondary to herniation of the stomach[28]. Because of the frequent association of other major injuries, ruptured diaphragm has been proposed as a marker of severe injury[24]. The clinical value of this is debatable, as the associated injuries are usually self evident.

Site of rupture

Older reports noted a great preponderance of left-sided rupture[26]. More recently, the ratio of left- to right-sided injuries has fallen and the incidence of right-sided injury is now generally reported at between 20 per cent and 50 per cent[7,13–16,18,22,25,27]. Possible explanations for this change include a greater awareness of the possibility of diaphragmatic rupture, an increasing incidence of severe upper abdominal trauma associated with motor accidents, and more rapid transportation and better initial care of patients with severe injuries, so that those with hepatic and major vein disruption now reach hospital alive[7,18,29,30]. Estrera *et al.*[31] found a 5·2 per cent incidence of ruptured diaphragm in 307 autopsies of road accident victims. These ruptures were evenly distributed between right ($n=5$), left ($n=5$) and bilateral ($n=6$) categories. Another autopsy series of 119 trauma victims[32] found a 7·6 per cent incidence of ruptured diaphragm, with four right-sided, four left-sided and one bilateral injury. These figures support the concept that ruptures with equal frequency on both sides, and that earlier series were biased by the excess prehospital mortality in right-sided injury.

Bilateral ruptures, and those involving the pericardium, are rare in patients reaching hospital alive because they are associated with severe injuries and high mortality. Occasional cases are recorded in several series and have merited case reports[33,34].

One area which is commonly ignored is the oesophageal hiatus. In 1971, Hood[26] found no report of hiatal involvement in a collected series of 239 left-sided ruptures, probably as a result of failure to note this injury independently in the reports reviewed. He drew attention to a report of two cases in which symptoms of reflux associated with hiatus hernia followed blunt abdominal trauma[35], but this association could well have been due to chance. Several authors have recorded hiatal disruption in 10–30 per cent of left-sided diaphragmatic injuries[17,36–38]. Pomerantz *et al.*[39] noted that nine of eighteen left-sided injuries affected the parahiatal area, and 'frequently' extended into the hiatus. McElwee *et al.*[14] found that seven of fourteen left-sided ruptures involved or extended to within 1 cm of the hiatus. Specific examination of the hiatus should therefore be made at operation to enable repair of any injury, in order to prevent possible late sequelae such as reflux oesophagitis and stricture.

Mechanism of rupture

The mechanism of injury is thought to be compression of the upper abdomen which results in a sudden large rise in intra-abdominal pressure which the diaphragm is unable to resist[14,39]. Shearing forces from lower thoracic compression may also contribute, and we have observed laceration of the diaphragm by the jagged end of a fracture rib. Avulsion of the diaphragm from its costal attachment is well described[27,39]. Several authors report that rupture most frequently occurs in the dome and that the tear passes posterolaterally in a radial direction[14,18,26,36]; this they attribute to an embryological weakness. In a study of bursting pressures of cadaveric diaphragms, the left side ruptured at a lower pressure than the right on eight of ten occasions, but the direction and site were not specified[40]. These authors found no consistent pattern of rupture in their clinical series. Others have also found that the site and direction of the tear is randomly distributed[7,31,37,38]. It seems that there is, in fact, no predeliction for one particular site, but that the frequency of injury is related to the size of the areas considered.

Clinical problems

As already stated, rupture of the diaphragm may be detected immediately after the injury on the first assessment in hospital, or as a result of delayed presentation during the initial hospital admission. Late presentation may occur at any time after discharge from hospital. Cases have been recorded as presenting after intervals of up to 48 years[16]. For the purposes of this review, the term 'early diagnosis' will be used to include patients diagnosed on admission or shortly thereafter, as this group poses different problems of diagnosis and management from those with a late presentation.

Early diagnosis

Most cases will be diagnosed by maintaining a high index of suspicion during the initial assessment and operative exploration of patients with severe blunt injuries, and by performing serial chest radiographs during the post-traumatic period. Clinical features of diaphragmatic herniation include respiratory distress, mediastinal shift, abnormal tympany or dullness (particularly over the lower part of the chest), and audible bowel sounds in the chest. All these signs are inconstant, and only the last is specific. In a patient on a ventilator, increasing inspiratory pressure, displacement of the mediastinum and a high 'diaphragm' on the chest radiograph (as opposed to depression of the diaphragm in tension pneumothorax) should alert the surgeon to the diagnosis.

Suggestive features on the chest radiograph include an apparently raised left hemidiaphragm with a gas shadow in the lower chest (particularly if the diaphragm appears to be thinned), fuzziness and blurring of the diaphragmatic surface and lower zone of the lung field, and collapse or consolidation of basal lung segments. Variable haemothorax, with drainage of blood into the peritoneal cavity in the erect position, has been described in a case of ruptured diaphragm without herniation[41]. It is necessary to take serial chest radiographs, as the first may be normal and initial management with intermittent positive-pressure ventilation may prevent herniation of abdominal viscera through the diaphragmatic rupture. The injury will become apparent when the patient breathes spontaneously and intrathoracic pressure falls below that of the abdominal cavity. Delayed rupture of the diaphragm has been described in a patient who underwent immediate laparotomy for intra-abdominal trauma. The diaphragm was carefully inspected and was found to be intact. On the third postoperative day the patient developed respiratory distress secondary to a hernia through a 12 cm defect in the left hemidiaphragm. Presumably, devitalized muscle softened and disrupted during the postoperative period[42]. Two other cases of possible delayed rupture have been recorded after normal chest radiographs immediately after injury. In one, there was epigastric discomfort, leading to a repeat chest radiograph 5 weeks after the injury, which demonstrated the diaphragmatic hernia[36]. The other patient developed acute left chest pain and dyspnoea 5 weeks after injury. Chest radiography demonstrated a diaphragmatic hernia[27]. These cases could also represent immediate rupture with delayed herniation, a sequence of events noted by many authors[14,16,17,32,38] and attributable to the fact that tears may be overlooked at operation[16]. The possibility of delayed rupture and the greater risk of immediate rupture followed by progressive herniation justifies a policy of obtaining daily chest radiographs for the first week after injury. Particular attention should be paid to radiological changes at the time that ventilatory support is discontinued and the patient returns to spontaneous ventilation. The return to negative intrathoracic pressure at this time favours herniation of abdominal viscera into the chest. Further radiographs should be obtained 1 and 3 months later in all patients suffering blunt trauma to the trunk to minimize the risk of a hernia remaining undetected.

When the stomach has herniated into the left chest and becomes distended as a result of cardiac and pyloric obstruction, the radiographic appearances can resemble a tension pneumothorax[26,28]. The diagnosis can be made by passing a nasogastric tube or by administering radiographic contrast material by mouth. The presence of either tube or contrast in the chest confirms the diagnosis of diaphragmatic hernia. One or other of these tests should be considered before draining a pneumothorax in any patient with blunt trauma to the trunk. Nasogastric intubation, by deflating the stomach, may be life saving[28]. If respiratory embarrassment is such that immediate chest drainage is required, care must be taken to avoid perforation of any herniated viscus in the thoracic cavity.

Other diagnostic tests which have been employed at this stage include the induction of a pneumoperitoneum with subsequent observation of a pneumothorax[14,26–29,38]. Brooks[28] describes the technique and its hazards. After a negative four-quadrant tap, 300–500 cm^3 of air is injected into the left lower quadrant of the abdominal cavity. An erect chest radiograph is then obtained. If there is a diaphragmatic rupture a pneumothorax will be evident. This test aggravates abdominal symptoms and produces shoulder tip pain, by diaphragmatic irritation, and so a negative test makes subsequent abdominal examination difficult. More importantly, the production of a pneumothorax may intensify ventilatory insufficiency, so that the pneumothorax should be aspirated promptly.

Diagnostic peritoneal lavage may be followed by hydrothorax or by recovery of lavage fluid from a chest drain[14,18,29]. Recently, experimental intraperitoneal or intrathoracic instillation of radio-isotopes has shown that the isotopes transgress the injured diaphragm[43]. Radio-isotope liver and spleen scan can also be used to detect herniation of these organs[44,45]. Visceral angiography may also show organ displacement but should be used only in cases in which aortic disruption is suspected[24,26,29,46]. Thoracoscopy[15] and laparoscopy[44,47] have also been said to be useful in the acute phase. Trunkey, delivering the British Journal of Surgery Travelling Fellowship Lecture at the 1987 meeting of the Association of Surgeons, stated that computerized tomography is 100 per cent accurate in the diagnosis of diaphragmatic hernia following blunt trauma.

Late diagnosis

Estimates of the frequency of missed diagnosis and subsequent late presentation are necessarily inaccurate. Late presentation is thought to occur in 5–30 per cent of diaphragmatic ruptures[13–15,17,28,31], but some earlier authors[3,4] found that as many as 50–62 per cent of cases presented late[3,4].

Diagnosis in the late phase can be difficult, because of the vague nature of the symptoms. The patient may not recall the previous trauma until the hernia has been diagnosed and specific enquiry is made. We have observed that, on occasion, the investigating physician may not associate the vague symptoms with previous trauma. Symptoms may be abdominal, with epigastric discomfort, colicky pain and nausea. Sometimes the patient may progress to acute intestinal obstruction[4,15,17,20,25]. Visset *et al.*[17] found abdominal symptoms only in patients with left-sided hernias containing stomach or bowel. The patient may have vague respiratory symptoms with recurrent chest infections and dyspnoea[3,4,25]. Dyspnoea may be more marked after meals[3]. Physical examination is unrewarding, although bowel sounds may be heard in the chest. Chest radiographs show basal shadows, which may contain loculated gas bubbles, or apparent elevation of the diaphragm. Barium studies are useful to demonstrate the herniated stomach, colon or small bowel[3,4,15] Other helpful investigations include radio-isotope imaging[45], ultrasound[14,48] and computerized tomography[14,44] which may demonstrate the liver or loops of bowel above the diaphragm. Laparoscopy is also useful in the elucidation of vague gastrointestinal symptoms[22,47]. Aspiration of bile from a herniated liver has been reported[49] but cannot be recommended as a diagnostic test!

Surgical approach

Early cases

The surgical approach to this injury can be rationalized by considering early and late injuries separately. With diaphragmatic injuries diagnosed during the early phase, there is a high incidence of injury to intra-abdominal organs, so that left-sided injuries should be approached through a laparotomy.

As noted above, significant intra-abdominal injuries requiring surgical repair are present in about one-half of the cases and, although some of these might be accessible through a left thoracotomy, thorough inspection of the abdominal contents to exclude injury of the duodenum, small bowel, colon, liver and contralateral hemidiaphragm is best done by laparotomy. All authors conclude that the rupture in the diaphragm can be closed equally well from above or below. If laparotomy is done first, only a small proportion will require thoracotomy in addition; for example, Ward *et al.*[27] found this necessary in one of 16 cases and Niville *et al.*[50] had to add thoracotomy on four occasions in 38 patients having initial laparotomy. Rodrigues-Morales *et al.*[18] found that extension into the chest to repair the defect was necessary in only one of thirty-five left-sided ruptures requiring laparotomy. However, in their total series of 58 patients having laparotomy for rupture of the diaphragm (left- or right-sided), 12 patients also required thoracotomy for cardiopulmonary resuscitation (5 cases) or control of intrathoracic bleeding (7 cases). Visset *et al.* [17] used laparotomy alone in 85 per cent of their cases of blunt injury to the diaphragm. In series which include a higher proportion of seriously injured patients thoracotomy is more frequently required[21–24]. Nevertheless, the recommendation of Estrera *et al.*[31] is justified, namely that laparotomy should be the approach in most cases, given that intra-abdominal injury is much more frequently encountered than intrathoracic injury. Indications for initial thoracotomy include massive haemothorax, the need to repair a flail segment, and suspected aortic rupture[18]. Oesophageal and tracheobronchial injuries are extremely rare in patients reaching hospital alive.

If thoracotomy has been performed and rupture is detected, the spleen, stomach, splenic flexure of the colon and left kidney should be inspected through the diaphragmatic defect. The liver should be palpated and the abdomen aspirated, and any suggestion of inaccessible abdominal injury should lead to laparotomy through a separate incision. All patients, whether having laparotomy or thoracotomy as the initial approach, should be prepared and draped into the 'corkscrew' position to allow exploration of the second body cavity if appropriate. The pelvis lies flat on the operating table, but the thorax and shoulders are rotated, and the uppermost arm is brought across the table on a support. Optimal access in both chest and abdomen is afforded by appropriate lateral tilt of the operating table.

Some authors advocate that right-sided injuries should be approached initially from the chest because the liver obstructs access to the diaphragm from below, and because the hepatic veins and vena cava are frequently injured, and are more easily repaired from above[13,25,29]. Abdominal exploration should follow if there is any suggestion of intraperitoneal injury[29]. In contrast, Rodrigues-Morales *et al.*[18] used laparotomy as the initial incision in 18 cases of right-sided rupture and one bilateral rupture. Only four of these patients required thoracotomy in addition. Flancbaum *et al.*[30] managed seven patients with right-sided ruptures, two with central rupture and one with bilateral rupture with initial laparotomy. None of the patients required thoracotomy. Meads *et al.*[51] recommend laparotomy as the initial approach in view of their finding in five cases that two patients managed with initial thoracotomy required laparotomy in addition, whereas three managed with initial laparotomy did not require thoracotomy.

Nevertheless, the feeling remains that a patient with a suprahepatic venous injury will be better served by initial thoracotomy so that immediate control of the haemorrhage can be obtained. These injuries may not become evident until the liver is reduced, opening up the venous injury and allowing massive bleeding[31]. The approach to right-sided diaphragmatic rupture should therefore be tailored to individual findings, with laparotomy being performed initially when the signs suggest massive intraperitoneal bleeding, but otherwise thoracotomy is the first step of choice.

Whichever approach is chosen, the patient must be prepared adequately and the surgeon must be ready to open the second cavity immediately if this is indicated. We have found that simultaneous laparotomy and thoracotomy can be performed satisfactorily without dividing either the costal margin or the diaphragm. These manoeuvres should be avoided as the former increases postoperative pain and the latter increases the risk of dehiscence of the diaphragmatic suture line.

In either right- or left-sided rupture, if a perforated viscus is found in the chest, thorough lavage of the thoracic cavity is required. This complication has a high morbidity and mortality, often leading to empyema. Ward *et al.*[27] recommend thoracotomy to ensure adequate lavage and drainage if perforation into the chest is found at laparotomy. They found a high rate of subsequent empyema when such injuries were managed by laparotomy and transdiaphragmatic irrigation of the thoracic cavity.

Late presentation

In contrast with early presentation, most authors agree that diaphragmatic hernias presenting in the late phase are best managed through a thoracotomy incision, although again the 'corkscrew' position should be used. Thoracotomy is preferred because there is no associated abdominal trauma to be dealt with, and intrathoracic adhesions are likely. While it may be possible to break down these adhesions through the diaphragmatic defect if an abdominal approach is used, it is easier and safer to do so through a thoracotomy, and laparotomy is hardly ever necessary for lysis of adhesions to allow reduction of the hernia[3,14,15,17,20,31,37].

Closure of the defect

There is no disagreement about the preferred method of closure of the defect. All authors recommend interrupted non-absorbable sutures to approximate the edges of the defect. This can be performed easily and without tension in almost all cases. One layer of full-thickness sutures or a two-layer repair have been used and appear to be equally effective. The incidence of recurrent herniation is negligible[4,16,25,37,40]. Late presentation is usually associated with a large well-established defect in the diaphragm. Although this defect has fibrous edges, it cannot always be easily approximated without tension. Consequently, prosthetic materials may be needed to close the defect[3,25,28,31]. Recurrence after this procedure has not been described.

Need for early diagnosis

The importance of making a correct diagnosis during the primary admission lies in the prevention of the late complications. Because of the negative intrathoracic pressure, progressive herniation is almost inevitable[7]. No case of spontaneous closure of a diaphragmatic laceration has been reported, although this would be unlikely, given that surgical closure usually follows once the diagnosis has been made. After a latent period, sometimes of many years, the patient may develop symptoms of gastric or colonic obstruction or of pulmonary compression. We have recently seen a 33-year-old man with a 2-year history of recurrent pneumonia and left basal consolidation, 16 years after a road traffic accident in which he sustained fractures of ribs and cervical vertebrae. The symptoms were secondary to pulmonary collapse caused by herniation of the transverse colon and omentum through a lateral defect of the left hemidiaphragm.

Intermittent gastric herniation with obstruction and subacute and acute obstruction of the large bowel are also described[26], but strangulation is less common after blunt injuries than after penetrating wounds[4,12], which tend to produce a smaller diaphragmatic defect[7]. When present, it is said that strangulation entails a much higher postoperative morbidity and mortality (25–66 per cent) than operations for uncomplicated diaphragmatic hernia[4] but this experience is not universal[13]. The incidence of such late presentations will be reduced if the surgeon maintains a high index of suspicion for diaphragmatic injury in all cases of abdominal and chest trauma, both during the initial surgical exploration and throughout the primary hospitalization and early follow-up period.

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Management of penetrating abdominal stab wounds

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The authors present the results of a therapeutic trial of the conservative or surgical management of penetrating abdominal stab wounds (PASW) based on clinical criteria. In a prospective series of 100 patients, 70 were treated non-operatively. Thirty patients were operated upon, twenty-one immediately and nine during the 48 h observation period. In five laparotomies no significant injuries were found. Morbidity was similar in both immediate and delayed laparotomy groups (3/21 versus *1/9). Acute alcoholic intoxication identifies a subgroup of patients that are difficult to evaluate and hence are more likely to be managed by laparotomy ($\chi^2 = 4{\cdot}056$,* P*$<0{\cdot}05$). The authors conclude that selective surgical management of PASW based on clinical criteria is an accurate and safe procedure.*

Keywords: Trauma, stab wounds, laparotomy

Until 1960, mandatory laparotomy was the accepted management of penetrating abdominal stab wounds (PASWs) when peritoneal penetration was established. The rationale was to avoid the risk of potential complications arising from a possible intra-abdominal injury in the absence of peritoneal irritation and/or evidence of haemorrhage.

However, Shaftan[1], in 1960, showed that a very high percentage of these patients did not have any significant injury within the abdomen; he concluded that laparotomy had been unnecessary in more than one-half of these patients and at the same time had caused significant morbidity. In a retrospective study performed in our Department of Surgery, we found the number of unnecessary laparotomies to be 63 per cent with a 19 per cent incidence of complications[2].

Shaftan's proposal has been opposed by some authors[3] and supported by others in subsequent publications[4–6]. As controversy still exists over the management of patients with PASWs, the aim of this prospective study was to assess the efficacy and safety of a therapeutic protocol for the management of PASWs, in which surgical intervention is based on clinical criteria.

Patients and methods

From April 1985 to November 1986 we have prospectively evaluated a total of 100 patients in the Emergency Unit of the University Hospital of Barcelona. All patients had a penetrating stab wound demonstrated by digital exploration of the wound, usually under local anaesthesia. There were 95 male and 5 female patients, ranging in age from 16 to 84 years, with a mean of 29·5 years. All patients had an intravenous line established, blood drawn for full blood count, creatinine, electrolytes and blood sugar, and abdominal X-ray. A full physical examination was performed in each case.

All patients in this study were treated under a selective management protocol based on clinical findings. Laparotomy was undertaken only after demonstration of one or more of the following signs: shock; uncontrolled bleeding from the wound or gastrointestinal haemorrhage, signs of peritoneal irritation (rebound tenderness or absent bowel sounds); evisceration of an intraperitoneal structure such as omentum or bowel, or pneumoperitoneum at the time of initial examination or during the observation period (*Table 1*).

Clinical evaluation was performed every hour for the first 3 h and at intervals after this up to 48 h. No patient in this study underwent peritoneal lavage for diagnostic purposes.

After initial evaluation, patients were placed into two categories. (A) immediate laparotomy; (B) 48 h observation. For the purposes of analysis patients in group (B) were divided thus: (B_1) no laparotomy during the admission period; (B_2) delayed laparotomy. Morbidity, mortality and hospital stay were evaluated in relation to the time of surgery. The incidence of surgical intervention was analysed in relation to the type of trauma (self-inflicted or not), other associated stab wounds (abdominal or thoracic) and acute alcoholic intoxication.

Statistical analysis was performed using two by two contingency and χ^2 method where appropriate.

Results

Of the 100 patients who entered the study, 70 were treated non-operatively. The most common site of the external wound was the left upper quadrant (44 per cent). The right upper quadrant and the epigastrium accounted for 15 per cent and 12 per cent, respectively. The organ most frequently injured was the small bowel (33 per cent of the injuries), followed by blood vessels (27 per cent), liver or spleen (18 per cent) and urinary tract (9 per cent).

Twenty-eight patients had a self-inflicted stab wound; fourteen patients came to the Emergency Unit with acute alcoholic intoxication; nineteen patients had more than one PASW.

Category A

Twenty-one patients (21 per cent) were operated on immediately for suspected intra-abdominal injuries. Indications for surgery were as follows: 11 patients for evisceration (omentum in 9 and small bowel in 2), 4 for haemorrhagic shock, 3 for uncontrolled wound bleeding, 2 because of peritoneal irritation and 1 because of pneumoperitoneum. Seventeen patients (81 per cent) had significant intra-abdominal injuries. Four had negative explorations or trivial injuries which did not require treatment (indications for surgery in these patients were omental evisceration and pneumoperitoneum) (*Table 2*). Morbidity was 14 per cent (3/21), (two cases of pneumonia and one of wound infection). There were no deaths; mean hospital stay was 8·8 days.

Table 1 *Clinical criteria of significant intra-abdominal injury*

1. Shock or persistent systolic pressure below 90 mmHg
2. Uncontrolled bleeding from the wound
3. Gastrointestinal haemorrhage
4. Evisceration of an intraperitoneal structure (omentum or bowel)
5. Signs of peritoneal irritation:
    - Absence of bowel sounds
    - Rebound tenderness
    - Abdominal rigidity
6. Pneumoperitoneum

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Table 2 *Results for 21 group A patients. immediate laparotomy*

	No of patients
Clinical criteria for exploratory laparotomy	
Shock	4
Wound bleeding	3
Evisceration	11
Peritoneal irritation	2
Pneumoperitoneum	1
Findings at laparotomy	
Small-bowel injury	6
Colon injury	3
Vascular injury	7
Kidney/ureteral injury	1
Splenic/liver injury	5
No significant injury	4

Category B

Seventy-nine patients (79 per cent) were placed in this category. Seventy (70 per cent) were treated non-operatively without complications and discharged within 2 days (group B_1). Nine patients (9 per cent), initially observed, underwent delayed laparotomy (group B_2). Indications for surgery were peritoneal irritation in eight patients and hypovolaemic shock in one. The average delay from admission to operation was 5·1 h. Eight patients had significant intra-abdominal injuries (*Table 3*) In this group (B_2), there was one false positive and one complication (11 per cent). The average length of hospital stay was 10·2 days and there was no mortality.

Overall results showed no false negatives (no patient was readmitted) and five false-positive laparotomies (5 per cent. four in category A and one in group B_2). There were no differences in morbidity (14 per cent *versus* 11 per cent) or hospital stay (8·8 *versus* 10·2 days) between immediate and delayed laparotomy groups.

Type of trauma

Twenty-eight patients had self-inflicted injuries; five of these patients (18 per cent) underwent operation. Although the incidence of surgical intervention in this group was lower than in the remaining 72 patients (35 per cent), the difference was not statistically significant ($\chi^2 = 1·564$; $P > 0·3$).

Number of abdominal wounds

Nineteen patients had more than one abdominal wound and in one-half of these patients (10/19) there was an indication for surgery. Although the incidence of surgical intervention was higher than in the remaining patients (20/81) the difference did not reach statistical significance ($\chi^2 = 2·73$) There was one false-positive laparotomy. The incidence of intra-abdominal injuries did not differ from the overall study group ($\chi^2 = 1·638$).

Acute alcoholic intoxication

Fourteen patients had a history of alcohol consumption before the injury; in nine an exploratory laparotomy was performed. Surgical intervention was more frequent in this type of patient ($\chi^2 = 4·056$, $P < 0·05$). It is of interest that in five of these nine patients surgical intervention was considered after a period (delayed laparotomy): therefore, five of the nine patients operated upon during the observation period were under the influence of alcohol. There were three false-positive laparotomies (21 per cent), an incidence similar to that of the overall total ($\chi^2 = 1·71$).

Discussion

Selective surgical management of PASWs is still controversial. The policy of mandatory exploration leads to many negative laparotomies—up to 53 per cent in some series. Results published to date suggest that selective surgical management, if correctly performed, is a safe procedure. Selective surgical management seems to significantly reduce the number of laparotomies (down to 30 per cent), as well as the mean hospital stay (4·1 days). Delayed laparotomy does not increase the morbidity compared with immediate laparotomy (3/21 *versus* 1/9, $\chi^2 = 0·06$).

Table 3 *Results for nine group B_2 patients· delayed laparotomy*

	No. of patients
Clinical criteria for exploratory laparotomy	
Hypovolaemic shock	1
Peritoneal irritation	8
Findings at laparotomy	
Stomach/small-bowel injury	5
Colon injury	1
Vascular injury	2
Kidney/bladder injury	2
Splenic/liver injury	1
No significant injury	1

The number of surgical interventions in our study group is 30 per cent, which is lower than the rate in Demetriades' series[7] and that reported by Lee and colleagues[8] A possible explanation could be that our group has a total of 28 self-inflicted injuries. We have not, however, been able to find any difference in the number of laparotomies ($\chi^2 = 1·564$) between the trauma and self-inflicted wounds.

In order to define a subgroup of patients with a higher risk of intra-abdominal injury we have evaluated two different factors: the number of abdominal wounds and the incidence of acute alcoholic intoxication.

The number of abdominal wounds is of no help in identifying patients at risk of intra-abdominal injury. Patients in acute alcoholic intoxication, however, were more frequently operated upon, the number of laparotomies being higher compared with those in the remaining patients ($\chi^2 = 4·056$, $P < 0·05$). Although there were more false-positive laparotomies in this group, this was not significant (3/9 *versus* 2/21). It has been suggested in various reports[7,9] that alcoholic intake does not influence the reliability of clinical abdominal assessment but our experience does not support this. Clinical assessment seems to be more difficult in this type of patient as peritoneal irritation is probably more difficult to evaluate.

We did not attempt to evaluate the diagnostic accuracy of different indications for exploration but, considering our results (diagnostic accuracy of 95 per cent), we suggest that peritoneal lavage is not necessary. Another problem is the significance of omental or bowel evisceration. Recently, some authors have reported the reliability of this clinical sign, with an incidence of intra-abdominal injury up to 75 per cent[10–12]. Our experience has confirmed a similar frequency (73 per cent). Other investigators[7,13–15] have safely managed omental or bowel evisceration by replacement within the abdominal cavity. It is difficult to discard mandatory laparotomy in such cases as the incidence of intra-abdominal injury is very high (73 per cent). In most contexts, however, we believe that we have confirmed the safety of restricting laparotomy to specific clinical indications.

Acknowledgement

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Case report

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True radial artery aneurysm

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Aneurysm of the radial artery is uncommon, and is usually the result of some local injury or infection. True arteriosclerotic aneurysm of the radial artery of the type that is common in the lower aorta and popliteal arteries does not appear to have been reported previously.

Case report

A 55-year-old local government officer presented with a 3-week history of pain and tingling in his right hand and a 1-day history of a lump in his upper right forearm. There was no history of trauma. His brother had died 2 years previously of an abdominal aortic aneurysm.

On examination there was a 2 cm diameter expansile swelling distally in the right cubital fossa: auscultation revealed no bruit. There was punctate ischaemia on the pulp of the right middle finger and splinter haemorrhages in the right index, middle and ring finger nails. He was normotensive, in sinus rhythm, the right radial pulse was normal and there were no other cardiovascular signs. A plain radiograph of the right elbow showed curvilinear calcification in a position corresponding to the lesion. A diagnosis of a proximal radial artery aneurysm with distal embolization was made, and this was confirmed by selective arteriography, which also showed digital vessel occlusion (*Figure 1*).

Exploration showed a small saccular aneurysm of the radial artery just distal to its posterior interosseous branch, which contained thrombus. It was excised and an end-to-end anastomosis was performed. The patient made an uneventful postoperative recovery.

Histological examination showed an atheromatous aneurysm. Culture of the sac was negative (including fungi).

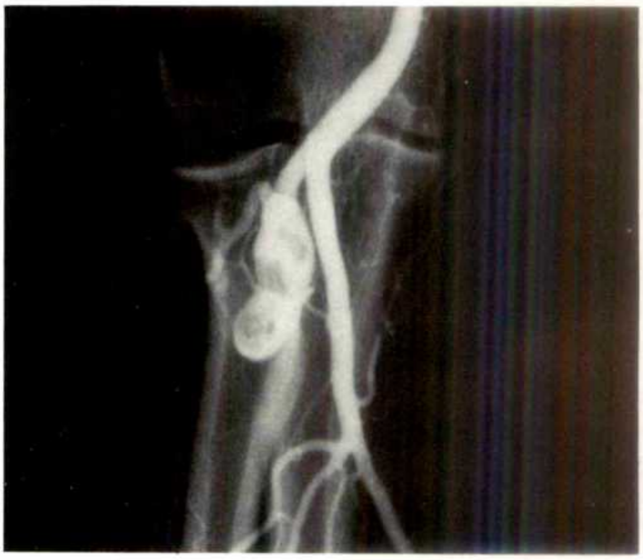

Figure 1 *Selective arteriogram of the right arm with radial artery aneurysm with thrombus*

Discussion

Distal embolization may be a presenting feature of any proximal aneurysm, but there are no previous reports in the recent literature of a true radial artery aneurysm at this site. More usually, they present as distal radial artery aneurysms at the wrist, commonly as a result of trauma[1-3].

Although this patient could not recall any significant local trauma, it is still possible that the vessel wall could have been weakened by previous blunt injury. He had no clinically apparent dilatation of any of his major vessels, nor any evidence of atheroma in the great vessels at arteriography, but it is interesting that there was a family history of aneurysmal disease.

Acknowledgements

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Surgical approaches to vertebral artery injuries

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Twenty patients with penetrating injuries of the vertebral artery who were treated as emergencies were subjected to the following operative approaches: five cases, Henry's approach (posterior) and modified Henry's approach (anterior); five cases, limited exposure and application of metal clips; four cases, plugging of the arterial defect with Oxycell or crushed muscle; three cases, control with ligatures and non-conventional exposure of the artery; one case, inflation of a balloon catheter within the vertebral canal; one case, repair of the lacerated first extraosseous part of the vertebral artery. One patient died from exsanguination on the operating table, before any repair was possible. The overall mortality was 20 per cent and the mean hospital stay 6·1 days. Thirty-five per cent of the patients presented with neurological complications, and 55 per cent left the hospital well. No advantage of Henry's classical approach over limited exposure and control with metal clips was shown, when mortality, hospital stay and long-term problems were compared. Because of its relative simplicity we suggest that the metal clipping of the vertebral artery, above and below the site of injury, is an effective technique that can be used to stop the bleeding. One case presented as a false aneurysm of the vertebral artery, following a stab wound. This was successfully treated with excision of the aneurysm and vertebrovertebral artery bypass, using a saphenous vein graft.

Keywords: Vertebral artery, neck, penetrating wounds, stab wounds

A policy of selective conservatism has been practised over the last 15 years at Baragwanath Hospital for the treatment of penetrating injuries of the neck in general and of the vertebral artery in particular[1,2]. The criteria shown in *Table 1* are currently being used. The results have shown this approach to be completely justified[1–3]. Penetrating injuries of the vertebral artery have been managed surgically in our institution for a number of years, using mainly the approach described by Henry[4] or a modified anterior approach[3]. The results have been very good when compared with previous experience[5,6].

Recently other surgical techniques have been put to the test at Baragwanath Hospital. This study is aimed at assessing their results, in comparison with the better known and established approaches.

Patients and methods

Twenty consecutive cases of acute penetrating injuries of the vertebral artery, explored as emergencies over the last 4 years, were included. The ages ranged between 20 and 35 years with a mean of 26 years. All the patients were men. The weapon was a knife in all cases.

The indications for urgent surgery included profuse bleeding with shock, pallor, low or unrecordable blood pressure, or a requirement of more than 1000 ml of IV fluids for pre-operative resuscitation, in eight cases. The same indications without any significant bleeding on arrival were used in another ten cases. In two cases the only indication was a large expanding haematoma in the neck.

Associated injuries were present in 13 cases as shown in *Table 2*. The entrance of the stab wound was in the right side of the neck in 12 cases, and in the left side in 6. The side was not specified in 2 cases. The entrance wound was anterior in 12, posterior in 6 and not specified in 2 cases.

It was not possible to establish the diagnosis of vertebral artery injury pre-operatively in any of the cases. In two cases however a fracture of the transverse process of a cervical vertebra was appreciated postoperatively, when the X-ray of the cervical spine was reassessed. In a single case death occurred on the operating table, before the vertebral artery was exposed and the bleeding controlled.

The following surgical approaches were used for the control of the injured vertebral artery:

1. Henry's approach and modified Henry's approach

Henry's approach (posterior approach). According to Henry[4] an incision was made along the anterior border of the sternomastoid and the muscle was either retracted or divided (*Figure 1*). The carotid sheath

Table 1 *Criteria for the exploration of penetrating injuries of the neck*

1. Profuse bleeding as expressed by:
   (a) Brisk bleeding from the wound
   (b) Shock
   (c) More than two bottles (c. 1200 ml) filled with blood after the insertion of an intercostal (chest) drain
2. Bruits or loss of distal pulses
3. Expanding haematoma
4. Bubbling of air through the wound
5. Blood stained sputa
6. Subcutaneous surgical emphysema without the presence of pneumothorax
7. Widened mediastinum on chest X-ray. Angiography should be carried out first, if available and the condition of the patient allows for the necessary delay
8. All injuries from high velocity missiles

Table 2 *Associated injuries*

	Number of cases
Haemothorax	1
Brachial plexus injury	2
Brachial plexus and internal jugular vein injury	3
Tear of the left subclavian artery and laceration of the cervical oesophagus (healed), severed recurrent laryngeal nerves bilaterally	1
Occipital artery injury	1
Stabbed internal jugular vein	4
Laceration of external carotid branches	1
Total	13

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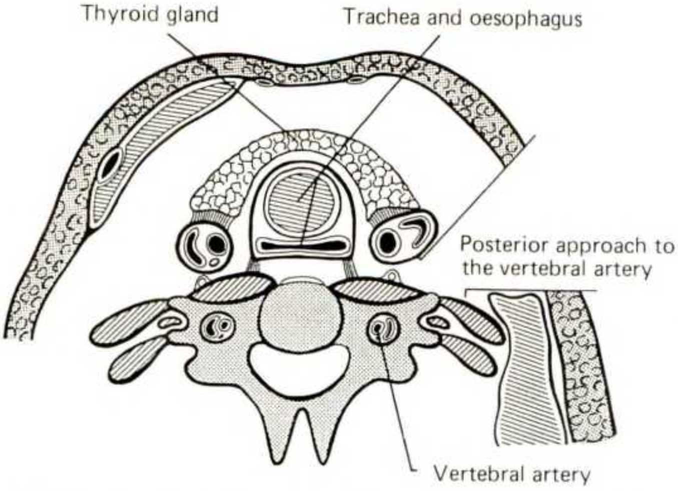

Figure 1 *Henry's posterior approach. The vertebral artery is shown within the osseous vertebral canal*

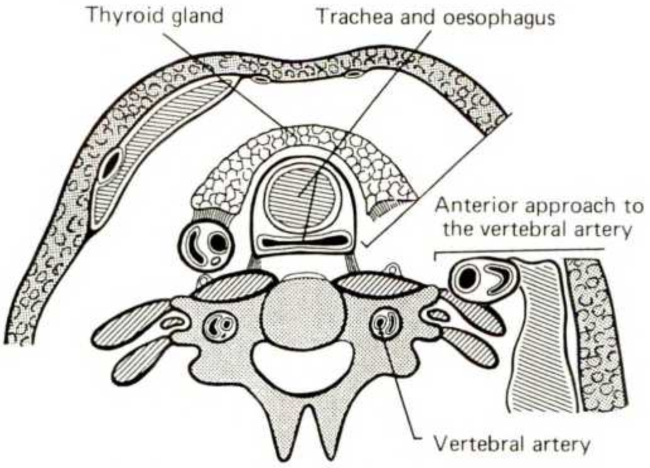

Figure 2 *Modified Henry's approach, anterior*

was retracted medially and anteriorly with the rest of the cervical viscera. Division of the omohyoid muscle allowed the space between the sternomastoid and the great vessels to open. By pulling the oesophagus further out of the way the prevertebral space was exposed widely, demonstrating a groove between the body of the cervical vertebra and the anterior tubercle of the transverse process. Between the probing finger and the vertebral artery lay only the longus cervicis (colli) muscle and the costo-transverse bar. The longus cervicis (colli) was swept off the bone, medially, with an osteotome. The costo-transverse bar, the thickness of a toe-nail, was removed with bone-nibblers to reveal the artery within the vertebral canal. It was always necessary to obtain control proximal and distal to the point of injury. Without distal control brisk bleeding resulted in all cases.

Modified Henry's approach (*anterior approach*)[3]. Using initially the same steps as for the posterior approach, the great vessels were retracted laterally and the cervical viscera medially (*Figure 2*). The space between the two was allowed to spring open by dividing the middle thyroid vein, and the prevertebral space was exposed. The rest of the operation was as described for the posterior approach. Before closure the head was allowed to return to a midline position without over-extension to avoid masking of the bleeding by over-extension only.

Henry's approach, anterior or posterior, was used in five cases.

2. Limited exposure and application of metal clips (five cases)

The exposure of the prevertebral space was the same as the one described for the anterior modified Henry's approach. The incision along the anterior border of the sternomastoid, however, was shorter, because less space was needed for the application of the metal clips. Mobilizing and displacing the longus cervicis (colli) muscle was not necessary. Two medium size metal clips (Hemoclip blue colour cartridge) were applied on the vertebral artery, above and below the injury at the same interspace. If that failed to control the bleeding a second set of clips of larger size (orange colour cartridge) were applied at the same places. If that also failed, then the heavier metal clips were applied in the interspaces above and below the one with the injury (*Figure 3*). This could be done over the intratransverse ligament without exposing the vertebral artery. Control of the bleeding was usually obtained this way. There is a wide space between the transverse processes which allows the placement of metal clips without having to remove the osseous part of the vertebral canal. *Figure 3* shows that the nerve roots run posterior to the vertebral artery, in a groove formed on the upper surface of the transverse process of the cervical vertebrae. If the clips are placed closer to the more superior of the two transverse processes, and from an anterior direction, the nerve roots can easily be avoided. This approach is much more rapid because it can be carried out through a small wound, with less extensive exposure. By merely feeling the space between the transverse processes with the index finger and guiding the metal clip applicator on the probing finger, the clips can be applied at the correct place. Proper displacement of the muscle is not necessary because the anterior limbs of the metal clip and that of the applying forceps are sharp enough to be introduced easily under the longus cervicis (colli) muscle. If some muscular fibres are caught between the limbs of the metal clip, enough compression is still applied to stop the bleeding.

3. Plugging of the arterial defect with Oxycell or crushed muscle (four cases)

The approach for the exposure was the same as with metal clipping. The only difference was that Oxycell or crushed muscle was plugged into the arterial defect or into the foramen transversarium outside the artery, instead of applying metal clips.

4. Control of the bleeding vertebral artery with ligatures, after non-conventional exposure of the artery

This approach was used in three cases.

5. Inflation of a balloon catheter within the vertebral canal

Control of the bleeding from the distal stump of the severed vertebral artery was achieved by introducing a balloon catheter into the vertebral canal, inflating the balloon and keeping it in place postoperatively. The proximal stump was ligated (one case).

6. Repair of the lacerated first part of the vertebral artery before it enters the vertebral canal (one case)

This approach has been described by Henry[4] and presented with no special problems.

One case presented as a false aneurysm of the right vertebral artery in a 19-year-old woman, after a stab in the neck. She experienced for 8 months after the injury a 'buzzing' 'pulsating' noise in the right ear. She was admitted to our ward at that time and a 4 × 4 × 4 cm pulsatile mass, which was producing a systolic bruit, was palpated in the anterior triangle of the right neck. She had a vertebral angiogram which showed a 3 × 3 cm aneurysm of the right vertebral artery, originating from the artery between the transverse processes of the 4th and 5th cervical vertebrae. She refused surgery. She was re-admitted 1 month later. The mass was unchanged in size. The noise and pulsation had disappeared, but she was very concerned about the cosmetic aspects of her problem, and requested resection of the aneurysm. Clinical assessment and laboratory work-up showed the patient to be in good state of health with

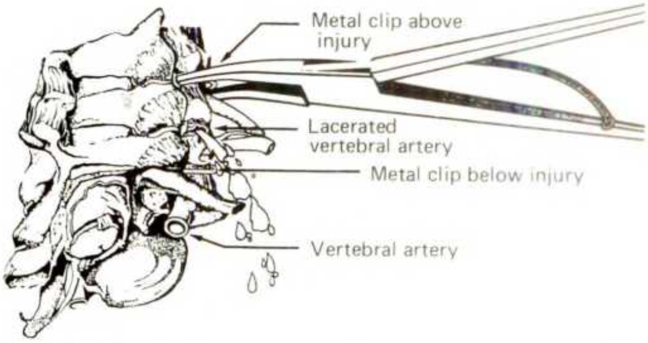

Figure 3 *Cervical vertebrae, ligaments intratransversarii, nerve roots, and injured vertebral artery. The correct placement of metal clips in the interspaces above and below are clearly demonstrated. Note the position of the metal clip close to the upper transverse processes*

Table 3 *Results*

Surgical method	Number of cases	Deaths	Quadriplegia	Mean duration of hospitalization (days)	Long-term problems	Experience of surgeon: Experienced surgeon	Experience of surgeon: Surgeon of less experience
Henry's approach	5	0	0	5·8	2	3	2
Metal clips	5	0	0	6·4	2	2	3
Oxycell or crushed muscle plugging	4	1	0	5·5	0	2	2
Foley's catheter in vertebral canal	1	1	1	—	—	0	1
Repair of first part of vertebral artery	1	0	0	11	1	0	1
Ligation	3	1	1	5·5	0	0	3
Cardiac arrest before repair	1	1	0	—	—	0	1
Total	20	4 (20 per cent)	2 (10 per cent)	6.14	5 (25 per cent)	7	13

Table 4 *Complications*

	Number of cases
None	10
Uncontrollable bleeding intra-operatively (death)	2
Quadriplegia (death followed)	2
Mild brain damage	1
Loss of deltoid and triceps	1
Decrease of motor function of deltoid, supinator, and rotator cuff	1
Bilateral vocal cord paralysis	1
Transient hoarseness	1
Pneumonia and median and ulnar nerve paralysis	1

Table 5 *Shock on arrival*

	Number of cases	Number of deaths	Length of hospitalization (days)
With shock on arrival	15	4	5·9
Without shock on arrival	2	0	4·5
BP not recorded	3	0	8
Total	20	4	

no other problems except for the aneurysm. She had a second bilateral vertebral artery angiogram, which demonstrated a patent right vertebral artery with a very small (0·5 × 0·5 cm) aneurysm at the same site as previously. It was assumed that the aneurysm was partially clotted. Cross-compression study of the vertebral arteries showed adequate filling of the right side of the brain while the right vertebral artery was compressed, and contrast was injected in the left vertebral artery. This was considered as an indication that potential ligation of the right vertebral artery would not cause any neurological problems. Balloon embolization was considered at the time but was abandoned as it would not solve the cosmetic problem. The patient underwent an exploration of the right neck instead, using the modified Henry's approach, extended somewhat to expose the extraosseous first portion of the vertebral artery. The artery was ligated above and below the aneurysm, and a reversed saphenous vein graft was interposed between the proximal and distal to the aneurysm vertebral artery stumps, in order to by-pass it. The aneurysm was then resected. The patient had an uneventful recovery and the result was functionally and cosmetically good. Postoperative digital subtraction angiogram showed a patent graft.

Results

Table 3 shows the results of each of the surgical approaches used. There was a 20 per cent mortality rate (4) in the 20 cases that underwent an emergency neck exploration. Two patients developed quadriplegia and death followed soon after. One patient had a cardiac arrest on the table before any type of repair was possible. Ten patients developed the complications shown in *Table 4*. Mortality, duration of hospitalization and long-term problems are recorded. The study is retrospective and the numbers are relatively small, therefore no attempt at statistical analysis is justified. It is obvious, however, that there are no clear differences in mortality and morbidity between the two main groups, Henry's approach and metal clipping. It must be pointed out that one death occurred in the group of patients where the plugging method was used, as a result of recurrent bleeding a few hours postoperatively. The mean duration of hospitalization was 6·1 days. This probably means that the patients who survived left the hospital early. Eleven of the twenty patients (55 per cent) left the hospital well with no further problems. Seven patients however (35 per cent) presented with some neurological problems, in four cases the result of an associated injury. The neurological damage was severe enough to cause death in two cases and long-term problems in five cases. Associated injuries are shown in *Table 2*. *Table 5* shows the influence of the presence of shock on arrival, on mortality and duration of hospitalization. The numbers are too small for statistical analysis but clearly there are no differences when one compares duration of hospitalization. In contrast to this, all the deaths occurred in patients who presented with shock on arrival. The experience of the surgeon does not appear to have been an important factor when comparing the results of Henry's approach and metal clipping (*Table 3*). It is true, however, that from the whole series all the deaths and the two cases of quadriplegia occurred in the hands of surgeons of 'lesser' experience. This makes a case for calling the most experienced surgeon available to take over the case in theatre when a vertebral artery injury is suspected or confirmed.

Discussion

Reference to *Table 3* makes it quite obvious that there were no significant differences in mortality and morbidity between the various surgical approaches used for the management of penetrating injuries of the vertebral artery. Henry's method with wide exposure and then ligation of the artery under direct vision is particularly attractive. The vertebral canal is only approached from the front and the nerve roots are easily avoided.

We are aware of a number of cases, before 1983, where a relatively inexperienced surgeon encountered great difficulty in obtaining wide exposure in a wound rapidly filling with blood. It is very difficult to compress the vertebral artery either digitally or with an instrument within the bony or ligamentous part of the vertebral canal, and the patient may exsanguinate. It is suggested therefore that when the relatively inexperienced surgeon is faced with this potentially lethal emergency, he should use the technique of metal clips.

Our limited experience with the use of the plugging technique does not allow us to express a firm opinion about its use. It is possible that the single intra-operative death that occurred when this technique was used could have been prevented by the use of an alternative method. Control with a balloon catheter as a temporary measure, until other injuries are handled, has already been described[7]. In our case it was left in place postoperatively, as a definitive method to control the bleeding vertebral artery. The plan was to remove it a few days later. This method was used in only one case, and the result was disastrous (quadriplegia and death). The mechanism of this death was not clear. The possibility of compression of the vessels supplying the spinal cord, or direct pressure on the cord, through a traumatic defect of the bony or ligamentous part of the spinal canal, must be considered.

Repair of the injured second intraosseous part of the vertebral artery has not been attempted in this series. Ligation of the subclavian artery was not used for the obvious reason that it does not control the bleeding from the distal end of the opened vertebral artery, which is usually very brisk.

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Announcement

Joint meeting of surgical colleges

Progress report on Intercollegiate Specialty Assessment

The four Royal Surgical Colleges in Great Britain and Ireland have, over the past 3 years, been giving earnest consideration to the need to make assessment of training in all the specialties of surgery more relevant to the demands of surgical practice now and in the years ahead. Much has been achieved by the collaborative work of the Joint Committee on Higher Surgical Training since 1967. That committee, representing the Surgical Colleges, the surgical specialist associations, and the Professors of surgery, has set the pattern in devising surgical training programmes at senior registrar level which give to the trainees experience of a wide range of clinical work at university and district general hospitals over minimum periods of 3–4 years according to the specialty.

Increasingly the Joint Committee has recognized the need to assess not only the quality of the training programmes but the extent to which those who occupy them have made the best use of the opportunities they offer. The four Colleges therefore decided the time had come to introduce a means of formal assessment of specialist trainees. Such intercollegiate assessments have been designed to establish not only the standard of performance of trainees but also the extent to which they have kept themselves up to date in studying the current literature. Assessments were introduced last year in plastic surgery and in urology and have taken the form of in-depth oral discussions of those aspects of the specialty with which the senior registrar or lecturer in the second or third year of a higher training programme should be familiar The assessments have been held on a voluntary basis but, after some initial hesitation, most higher trainees have submitted themselves as candidates and most have been successful at the first attempt. Discussions are now in hand to introduce similar assessment procedures in general surgery and in the other specialties including those for which the Edinburgh College has introduced specialty Fellowship examinations almost a decade ago (orthopaedic surgery, neurological surgery and cardiothoracic surgery). It is anticipated that the experience gained through these intercollegiate assessments will facilitate an improved review of the training programmes.

Concurrently with this initiative the four Surgical Colleges are studying a revision of their existing Fellowship examinations with a view to adapting them to a new continuum of postgraduate surgical examination and assessment and in order to make them more relevant to future surgical practice While there is no intention of making the present Fellowships intercollegiate—indeed the Colleges are anxious to preserve the identity of their own Fellowships and believe that there is value in that degree of diversity—they are keeping in close touch with each other to ensure that the standards of the four Fellowships remain comparable. The common objective will be to develop reciprocally recognized Fellowship examinations of a high standard in the basic sciences relevant to modern surgery and in the basic surgical principles that are necessary for entry to higher training in each and every surgical specialty. The diplomas of Fellowship will have reciprocal status and, after further specialty training, will permit entrance to the Intercollegiate Board Assessment procedure

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Doppler ultrasonography in the diagnosis of acute scrotal pain

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Pre-operative Doppler ultrasonography was performed on 41 patients who underwent an emergency scrotal exploration because of the clinical suspicion of a testicular torsion. The final diagnoses were testicular torsion in 18 patients, epididymitis in 15 patients and torsion of a testicular appendage in 8 patients. An unequivocal indication as to the presence or absence of a testicular torsion was obtained in 31 patients (76 per cent), an equivocal result was obtained in 5 patients and in 5 patients the examination was unsatisfactory. The sensitivity and specificity of the investigation for the diagnosis of testicular torsion were 67 per cent and 83 per cent respectively, and the predictive value of either a positive or negative result was 100 per cent. Our results suggest that the use of Doppler ultrasonography could reduce the incidence of unnecessary operations without incurring the risk of reduced testicular salvage.

Keywords: Spermatic cord torsion, epididymitis, scrotum, Doppler ultrasonography

Urgent treatment for torsion of the testis is necessary if the testis is to be preserved. The inaccuracy of clinical diagnosis is now well recognized, and it is generally advised that all boys and young men with acute scrotal pain should undergo an immediate scrotal exploration unless there is unequivocal evidence of infection. This aggressive approach has almost certainly led to increased testicular salvage, but has also resulted in 18–65 per cent of operations being performed unnecessarily[1,2]. The need for greater diagnostic accuracy has led to the introduction of radionuclide imaging and Doppler ultrasonography to detect testicular ischaemia. The accuracy and limitations of radionuclide imaging have been established by careful evaluation[3–5], but Doppler ultrasonography has been subject to less critical assessment and its value remains unclear. We report here the use of Doppler ultrasonography in 41 patients who underwent an emergency exploration of the scrotum because of the suspicion of a testicular torsion.

Patients and methods

Between November 1985 and April 1987, 60 patients aged between one and 35 years underwent emergency scrotal exploration because of the suspicion of a testicular torsion. A pre-operative Doppler examination was performed on 41 patients, and these patients were selected solely by the availability of one of us (K.I.B. or K.S.) to perform the examination. The Doppler examinations were only performed after the decision to operate had been made by the responsible clinicians and these clinicians were not informed of the results. The final diagnoses were obtained from the surgeons who had performed the operations.

The Doppler examinations were performed using a Sonicaid Vascular Flow Detector, Model BV1029. The unaffected testis was fixed in position and the transducer pressed gently against the anterior surface of the testis to compress the vessels in the scrotal wall. The transducer was pointed towards the lower pole of the testis and moved slowly over the anterior surface until an audible signal corresponding to pulsatile arterial blood flow was heard. When the maximum signal had been obtained a funicular compression test was performed by briefly compressing the spermatic cord. The test was considered positive if compression resulted in the disappearance or diminution of the signal and indicated that the signal had originated from flow in the arteries of the testis rather than from those of the scrotal wall. The affected testis was then examined in the same way and the intensity of the maximum signal compared with that of the unaffected testis. The intensity of the signal (described as absent, reduced, equal or increased), and the results of the testicular compression test were recorded.

The patients were allocated to one of the following diagnostic groups according to the Doppler results from the affected testis

Failure. Unsatisfactory examination (including inability to perform a funicular compression test).

Testicular torsion. Absent or reduced signal.

Not testicular torsion Equal or increased signal with a positive funicular compression test.

Equivocal Equal or increased signal with a negative funicular compression test.

The data and time of all admissions were obtained from the admission registrar of the Accident Department. Normal working hours were defined as 9.00 a.m. to 5.00 p.m. Monday to Friday, excluding public holidays.

Results

The ages and final diagnoses of the patients who underwent a Doppler examination are shown in *Table 1*. Eighteen patients had a testicular torsion and viable testes were salvaged in 14 patients (78 per cent). One viable testis was thought to have undergone a spontaneous reduction during the induction of anaesthesia. Bilateral testicular torsion or the spontaneous reduction of a torsion before the Doppler examination did not occur in the study group. The diagnosis of acute epididymitis was made mainly on the operative finding and by the exclusion of other causes of acute scrotal pain. Microbiological confirmation of the diagnosis was obtained infrequently, but other causes of scrotal pain (e.g. acute hydrocele, tumour and idiopathic scrotal oedema) were not encountered in the patients studied. The age distribution and proportion of patients with testicular torsion of the study group were similar to those of the

Table 1 *Age and final diagnosis of patients*

	Diagnosis		
Age (years)	Testicular torsion	Torsion of testicular appendix	Epididymitis
1–6	1	1	3
7–12	6	7	2
13–18	7	0	6
>18	4	0	4
Total	18	8	15

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Table 2 *Results of Doppler examination*

	Final diagnosis		
Doppler result	Testicular torsion	Torsion of testicular appendix	Epididymitis
Testicular torsion	12*	0	0
Not testicular torsion	0	7†	12‡
Equivocal	3	0	2
Fail	3	1	1

* 3 decreased signal; 9 absent signal; † 2 increased signal; 5 equal signal, ‡ 5 increased signal; 7 equal signal.

complete group of patients operated upon during the period of the study.

The results of the Doppler examination are shown in *Table 2*. The five failures, all in patients under the age of 13 years, occurred because the examination could not be performed without producing excessive discomfort. The sensitivity of the investigation for the diagnosis of testicular torsion was 67 per cent, and the predictive value of a positive result was 100 per cent. The specificity of the investigation (i.e. the proportion of patients without testicular torsion correctly diagnosed) was 83 per cent and the predictive value of a negative result was 100 per cent. Thirty of the sixty patients (50 per cent) were admitted outside normal working hours.

Discussion

The previous reports on the use of the Doppler stethoscope have produced conflicting results. Early studies found the investigation to be completely accurate[6–9], but only small numbers of patients were examined and examples of misdiagnosis were later reported[10,11]. In larger and more controlled studies, Brereton reported that the investigation was inaccurate in 25 per cent of patients in a paediatric practice[12], but Rodriguez *et al.* found the technique to be clinically useful in both boys and young adults[4]. We found that an unequivocal indication as to the presence or absence of a testicular torsion could be obtained in 76 per cent of the patients, and when such an indication was obtained it was invariably correct. Our results suggest that the Doppler stethoscope could be useful in the diagnosis of the acutely painful scrotum, but the precise technique and limitations of the examination need to be understood clearly.

The precise technique of the Doppler examination is of critical importance if misdiagnosis is to be avoided. Most, if not all, of the reported cases of misdiagnosis can probably be attributed to faulty technique. Testicular torsion can be diagnosed incorrectly as epididymitis if a pulsatile signal, originating from either the inflamed scrotal skin or the testicular artery proximal to the torsion, is mistakenly interpreted as arising from the testis. These errors can be avoided by applying a funicular compression test[7] and by pointing the transducer towards the lower pole of the testis[4]. Our study is the first to use both these techniques and misdiagnosis of a testicular torsion did not occur. The main limitation of the investigation is that in the absence of testicular ischaemia a diagnosis cannot be made. Of particular importance is the inability of the Doppler examination to distinguish between epididymitis and conditions which require operative treatment such as torsion of a testicular appendage or a testicular torsion which has undergone spontaneous reduction. Misdiagnosis of these conditions can only be avoided by careful clinical assessment. Another limitation of the technique is that the presence or absence of a testicular torsion can only be diagnosed unequivocally in 76 per cent of patients. A satisfactory examination cannot always be performed on young boys and an equivocal result is sometimes obtained from longstanding testicular torsions or severe epididymitis.

We suggest that all patients who are strongly suspected of having a testicular torsion should undergo an urgent scrotal exploration. The Doppler examination (or any other investigation) is probably of little value in the management of these patients except perhaps to monitor attempts at preoperative manipulative detorsion. The investigation is probably of greatest value in the management of patients who are thought not to have a testicular torsion, but in whom the condition cannot be excluded with confidence on clinical grounds. The Doppler examination will demonstrate the absence of testicular ischaemia in many of these patients and unnecessary operations can be avoided. We emphasize that a careful clinical assessment is necessary for the safe interpretation of the Doppler results. The investigation seems to be of most use in patients over the age of 15 years, because in these patients a satisfactory examination can usually be performed and torsions of testicular appendages occur only rarely.

We found the Doppler examination to be rapid, simple and easy to learn. The investigation has been shown to be less accurate than the radionuclide scan[4] but, unlike the scan it is inexpensive, its use is not restricted to the major centres, and it does not delay treatment. The latter point is of particular importance as, in our study, 50 per cent of the patients presented outside normal working hours. Our results suggest that careful use of the technique could reduce the number of unnecessary operations without incurring the risk of reduced testicular salvage.

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High prevalence of abdominal aortic aneurysm in men with peripheral vascular disease: screening by ultrasonography

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A study was carried out to see if an ultrasonic examination of the abdominal aorta was indicated in every patient who attended an out-patient clinic with peripheral vascular disease (PVD). One hundred consecutive patients were studied and compared with a control group. The incidence of abdominal aortic aneurysm (AAA) in the control group was 2 per cent. In the study group, the male patients had an incidence of 20 per cent of aneurysm and ectasia, while the female patients had an incidence of 12 per cent. Of all the abnormal aortas found by ultrasound, only 31 per cent were palpable clinically. Two aneurysms that required operation were found, while the remainder are to be followed by regular ultrasound assessment. Further studies are necessary to conclude if screening of a high risk group, such as patients with PVD, is worthwhile.

Keywords: Aortic aneurysm, ultrasonic diagnosis

The need for early surgery of abdominal aortic aneurysm (AAA) is now widely accepted among trained vascular surgeons[1–3] and the logical extension of this is to detect, by screening, the aneurysm at an early, asymptomatic stage. AAA usually presents as an incidental finding, but it may suddenly rupture, with no previous symptoms[3]. Clinical examination will detect 90 per cent of aneurysms >6 cm diameter, but becomes very inaccurate for smaller aneuysms[3]. It is well recognized that even small aneurysms stand a significant chance of rupture within a number of years[1,4]. Darling *et al.*[1] stated that aneurysms 4–7 cm diameter stood a 25 per cent chance of rupture, while those <4 cm diameter had a 9·5 per cent chance of rupture. Cronenwett *et al.*[4] confirmed that small aneurysms rupture frequently. Ultrasonography is extremely accurate in identifying AAAs, therefore we decided to investigate whether a screening programme of a possible high risk group, patients with PVD, using this method was of any value. The results show features that have important implications for the detection and management of small AAAs.

Patients and methods

We have performed an abdominal aortic ultrasound examination on 100 consecutive patients seen in our vascular clinic These patients, the study group, have had a new clinical diagnosis of symptomatic occlusive PVD made by one consultant (A.P.W.) and substantiated by Doppler pressure studies. Routine clinical examination included palpation for any possible AAA

Ultrasonography was carried out using a static grey scale B scanner with a 3 5 MHz probe in most cases. In a few patients commercially available real time equipment was also used. All the examinations were done by the same consultant radiologist (J.M C W.), or a specially trained senior radiographer under his supervision. Several anteroposterior (AP) measurements of the aorta were taken until a maximum diameter was determined. The AP diameter was taken to be the widest AP diameter at right angles to the long axis of the aorta. This measurement was taken from the outer wall echo of the anterior aortic wall to the echo reflecting the inner margin of the posterior wall, this is a standard technique for ultrasonic measurement of aortic size[5], as there are constant and reproducible bright echoes at these points. A measurement was also taken above the level of the renal arteries, and the whole longitudinal outline of the aorta observed for the presence of any aneurysm.

For the purposes of this study of the aorta an aneurysm was defined as a localized dilatation. There have been attempts to quantify the diagnosis of an aneurysm and Cronenwett *et al*[4] defined it as an enlargement of the AP or transverse infrarenal aortic diameter more than 1·5 times the diameter of the aorta at the renal arteries. However many people disagree with this definition and most publications on the subject do not define an aneurysm. In addition, an ectatic group was identified and defined as a generalized dilatation of the aorta from the diaphragm to the bifurcation with a minimum diameter of 3 cm. This figure was chosen, despite no accepted definition of ectasia, as it was felt that at this diameter, even for large patients, the aorta is abnormally large and could be regarded as pathological with a tendency for future aneurysm formation.

A 'control' group was used to see if the prevalence of AAA in a group not noted to have symptomatic PVD was significantly different. We studied 100 consecutive patients with bronchogenic carcinoma referred for pre-operative staging liver ultrasound. The additional time required to scan the aorta was minimal in these patients who were undergoing ultrasound in any case.

Student's *t* test was used for statistical analysis.

Results

The 100 patients were seen over a 15-month period starting in February 1984. The presentations were as follows: claudication 82 per cent, rest pain 11 per cent, carotid bruit and transient ischaemic attacks 2 per cent, other aneurysm 3 per cent, and ischaemic ulcer 2 per cent.

Men and women have been divided into separate groups as it was found that the female aorta was smaller and had a lower incidence of aneurysm (*Figures 1* and *2*). The study and control groups were well matched for age and sex (*Table 1*). There were unsuccessful examinations in up to 18 per cent of the four groups, due to either obesity or bowel gas obscuring vision.

In the male study group (75 patients), nine aneurysms were identified by ultrasound but only five of these were detected clinically and none smaller than 4·2 cm was felt. In this same group, four ectatic aortas were discovered. Thus, in the male study group, 20 per cent of successfully examined aortas were found to be aneurysmal or ectatic. In the female study group, one aneurysm and two cases of ectasia were found. Thus, 12 per cent of cases were abnormal in the females, but none of them was detected clinically.

The control group was markedly different with only two cases of male aneurysm and no other abnormal aorta.

The mean diameter of the aorta in the male study group was 2·7 cm, and this compared with 2·3 cm in the control group (no significant difference, $P > 0.05$). For females, the mean diameter

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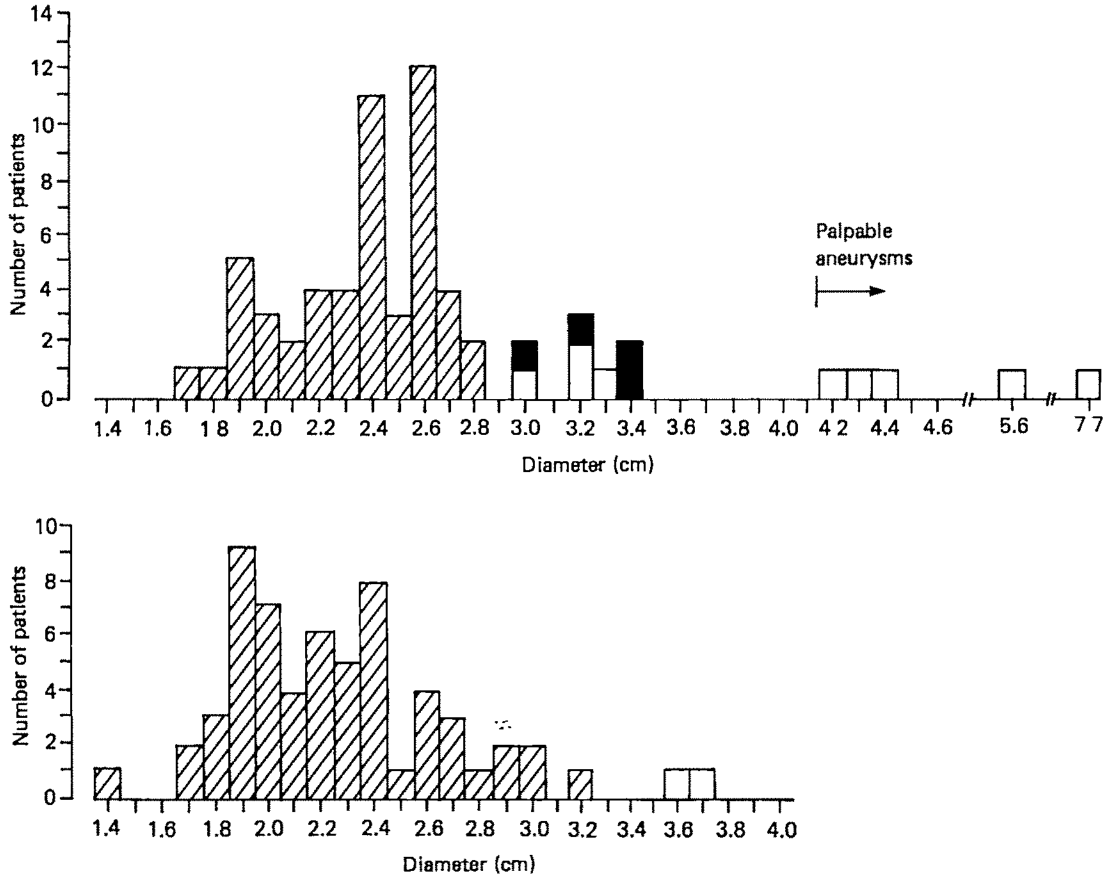

Figure 1 *Diameter of male abdominal aorta Study group (above). 75 patients (10 failed), 9 aneurysms* □, *4 ectasiae* ■, *mean diameter=2·7 cm, mean age=63·2 years. Control group (below). 74 patients (13 failed); 2 aneurysms* □, *mean diameter=2·3 cm, mean age=64 4 years*

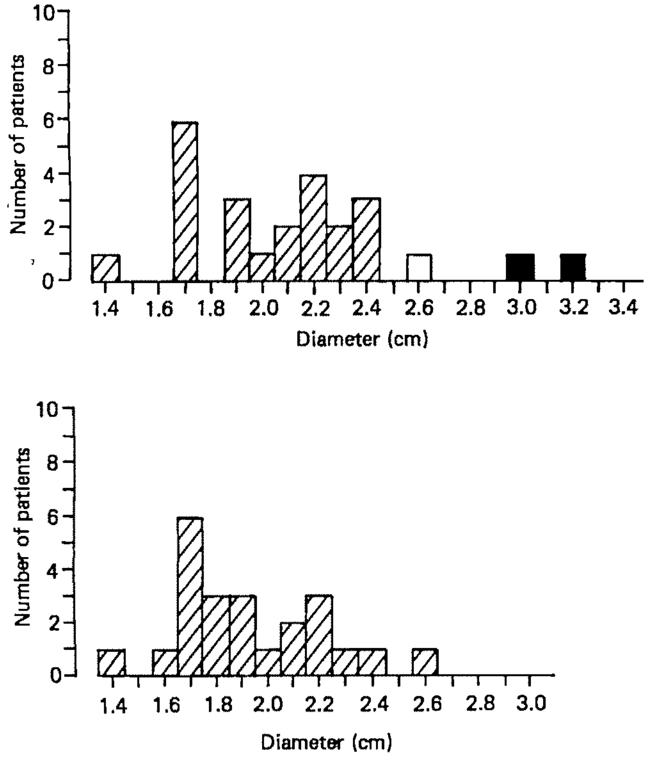

Figure 2 *Diameters of female abdominal aorta. Study group (above). 25 patients, 1 aneurysm* □, *2 ectasiae* ■, *mean diameter=2 1 cm, mean age=66 4 years Control group (below) 26 patients (3 failed), no aneurysms, mean diameter=1·9 cm, mean age=64 1 years*

Table 1 *Summary of results*

	Men		Women	
	Study $n=75$	Control $n=74$	Study $n=25$	Control $n=26$
Failed examination	10 (13%)	13 (18%)	0	3 (12%)
Aneurysm	9 (14%)	2 (3%)	1 (4%)	0
Ectasia	4 (6%)	0	2 (8%)	0
Mean diameter (cm)	2·7	2·3	2 1	1 9
Diameter range	1 7–7·7	1·4–3 7	1·4–3·2	1 4–2·4
Mean age (years)	63·2	64 4	66 4	64·1
Age range	39–90	34–86	47–84	52–81

in the study group was 2·1 cm, while in the controls it was 1·9 cm (no significant difference, $P>0{\cdot}05$).

If all the abnormal aortas are excluded, then the mean diameter of the male study group was 2·4 cm, and for the controls 2·3 cm. For the females, the same exclusions gave a mean diameter for the study group of 2·0 cm and controls 1·9 cm.

When considering just the aneurysms, only 50 per cent were palpable clinically. If all abnormal cases are considered, then only 31 per cent were suspected clinically. Thus aneurysmal and ectatic aortas are common in this selected group of patients, but the abnormal pathology was detected in fewer than one third of cases.

Discussion

Elective surgery for AAA is safe with a perioperative mortality of certainly <5 per cent[3,6], therefore it is important to discover aneurysms before they become symptomatic or rupture[7]. Screening of the general population is not feasible because of the large numbers involved[8], but a policy of screening a high risk group may be cost-effective.

The incidence of AAA in the older general population is 2–3 per cent[9,10], but these figures were defined by autopsy studies. Twomey *et al*[11] and Cabellon *et al.*[12] have identified high risk groups for AAA. To our knowledge, no published study has attempted to define the prevalence of AAA in the typical PVD patients presenting to a vascular clinic, that is, predominantly male patients with intermittent claudication.

The incidence of aneurysm in the control group agrees with the published data of autopsy studies of 2 per cent. However our control group all had bronchogenic carcinoma and were all smokers, but none was known to have symptomatic PVD.

The distribution of 75 per cent men, 25 per cent women in symptomatic PVD agrees with the accepted figures for this. Ten aneurysms were identified, but only two of these were 'large' and many of the small ones were just at the beginning of the aneurysmal stage. However it is well known that 'small' aneurysms can rupture[1–4,13] so these should not be ignored. It was noted that three patients were aged over 80 years, but age alone should not necessarily be a contraindication to operation[2,4].

Six cases of ectactic aorta were defined. Rutherford[3] states that an ectatic aorta is much more likely to rupture than a normal aorta and, indeed, probably becomes aneurysmal. Thus 16 abnormal aortas were identified in our study group and represent a prevalence of 20 per cent in men and 12 per cent in women

Only 31 per cent of the abnormal cases were detected clinically. If a screening policy is to be successful, then the smaller AAAs must be identified. However, clinically, all AAAs $>4{\cdot}2$ cm were palpable.

There was no doubt that the two large aneurysms in our study group needed surgery[2,4,14,15]. We were left with the problem of what to do for the remaining eight aneurysms and six ectasiae. Aortic aneurysms increase in size by about 0·5 cm per year[15,16] and ultrasonography is a relatively cheap, quick, non-invasive and accurate[17–19] method to follow this. By observing the aorta at regular intervals, the ideal time for operation can be decided, but one should be wary that the occasional aneurysm suddenly becomes larger[4] and ideally an ultrasound examination should be performed every 3–6 months.

Our policy for our eight cases of aneurysm and six ectasia is to follow them up every 6 months with clinical and ultrasound examinations. Each case will present different problems and thus the diameter of the aorta would not be an absolute indication of whether to operate or not. Certainly if the aneurysm were to become symptomatic or rapidly enlarge, then operation would be strongly indicated. There is no unanimity among vascular surgeons about the size of an AAA above which surgery becomes mandatory, although most would operate on AAAs $\geqslant 5$ cm.

This pilot study has defined a high risk group of patients for asymptomatic AAA but does not demonstrate any benefit to the individual patient as yet. If one believes that the risk of rupture of small AAAs can be significant, and non-urgent operative mortality is <5 per cent, then surgery should be offered to patients with small AAAs. Ultrasound has been shown in this study to diagnose small aneurysms not suspected clinically. However the size of these aneurysms falls within a 'grey area' where the benefits of early operation may be considered marginal, if any. Further studies are needed on larger numbers of patients with a lengthy follow-up period to see if any benefit can be gained from early detection. Only by this method can the cost-effectiveness of screening of this high risk group be determined.

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Ultrasound mammography in the management of breast cancer

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In this centre, ultrasound mammography has been shown to be more accurate in elucidating the nature of palpable breast lesions than X-ray mammography. A prospective study was devised to determine whether this accuracy could be translated into improved management of patients with breast carcinoma. A total of 223 patients with palpable breast masses were assessed by clinical examination, imaging (X-ray and ultrasound mammography) and aspiration cytology. Each was scored on a five-point scale and treatment was planned according to the total score. According to the protocol, an adequate total score would permit definitive surgery avoiding frozen section. By using sonography rather than radiology, the number of correct diagnoses could be improved by 25 per cent. This was because the greater sensitivity of ultrasound (92·8 per cent) compared to X-ray mammography (82·5 per cent) was reflected in a higher total score, which was sufficient to allow definitive surgical treatment without prior histological confirmation of diagnosis.

Keywords: Breast cancer, ultrasound mammography, X-ray mammography

The 'triple assessment' system is an established method in specialist centres for collating information from clinical examination, X-ray mammography and aspiration cytology to provide an accurate diagnosis of malignancy without histology[1–3]. We have used a scoring scheme to rationalize treatment according to the results of these methods of assessment. This scheme has significantly reduced the frozen-section rate, thus making more efficient use of operating time and enabling better pre-operative counselling[4].

The scoring scheme, although of considerable clinical benefit, has certain limitations. For example, some patients have a mass, which subsequently proves to be malignant but which is not visualized by X-ray mammography because it is obscured by radiological density. Thus it is not ascribed a score high enough to permit definitive surgical treatment without prior biopsy. In other patients, X-ray mammography does not recognize a lesion as malignant because, like any investigation, its sensitivity is limited.

Ultrasound mammography is capable of imaging the radiologically dense breast[5] and has a very high sensitivity for carcinoma[6–8]. A study was undertaken to compare ultrasound and X-ray mammography as the imaging method in the scoring scheme, to determine whether these capabilities of sonography could be translated into an improvement of clinical management.

Patients and methods

Scoring scheme

A total of 223 patients over the age of 35 who presented to the Breast Clinic with a palpable mass were investigated by clinical examination, ultrasound mammography, X-ray mammography and aspiration cytology. Each of these was scored on a five-point scale (-2 definitely benign, -1 probably benign, 0 inconclusive, $+1$ probably malignant, $+2$ definitely malignant). Patients with scores between -6 and -1 were treated by excision biopsy, scores between 0 and $+3$ required 'Trucut' biopsy or occasionally frozen section, and scores between $+4$ and $+6$ were treated by definitive surgery.

Histology was available on all the patients.

This scoring system allows an objective comparison of the effect of each imaging method on the treatment of the patient.

Clinical examination

Each patient was examined in the Breast Clinic by either a consultant or a senior registrar

Ultrasound

A Philips 7100 Static B Scanner was used for the ultrasound examination. A 7·5 MHz transducer was applied directly to the skin, scanning at 2 mm intervals over the breast mass. The investigation took about 5 min and was performed and interpreted by one of two radiologists with an interest in breast disease.

X-ray mammography

This was performed using a Senograph X-ray set with Kodak Min-R film; standard craniocaudal and lateral–oblique views were taken. Bilateral mammograms were routinely undertaken since screening of the contralateral breast is important[9]

Aspiration cytology

A 21 gauge needle and disposable syringe mounted on a Cameco syringe holder were used. Suction was applied as the needle was introduced into the lesion several times. The contents of the syringe were then expressed on to a slide, stained and fixed, the slides were interpreted by a cytopathologist who was not aware of the clinical findings or imaging reports.

Results

Sensitivity

Histopathological confirmation of diagnosis was available on all 223 patients in the study. There were 166 malignancies and 57 benign lesions. The sensitivity of each method for malignancy is displayed in *Table 1*.

Two figures were given for each sensitivity. The score 0 for X-ray mammography would usually denote that the breast is radiologically dense so that malignancy can be neither confirmed nor denied. The score 0 for ultrasound mammography or clinical examination denotes that a solid, focal lesion has been detected which cannot be classified as malignant or benign. The score 0 for aspiration cytology is given for an inadequate sample.

Therefore, the sensitivity figure in *Table 1*, which is based only on $+1$ and $+2$ scores, describes the ability to make a true positive diagnosis, whereas that figure which also includes the score 0 denotes the ability to suggest the possibility of malignancy as well as a positive diagnosis.

The patient with malignancy for whom ultrasound mammography ascribed a score of -2 had a medullary carcinoma. This reason for diagnostic error is discussed below.

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Table 1 *A total of 166 proven malignancies: distribution of scores for each method of assessment and resulting sensitivity for malignancy*

Score	Clinical examination	X-ray mammography	Ultrasound mammography	Aspiration cytology
−2	0	0	1	0
−1	16	13	5	11
0	11	16	6	16
+1	64	50	42	36
+2	75	87	112	103
Sensitivity (score +1 or +2)	83·7%	82·5%	92·8%	83·7%
Sensitivity (score 0, +1 or +2)	90·4%	92·2%	96·4%	94·0%

Table 2 *Combined sensitivity for malignancy*

Clinical	X-ray mammography	Ultrasound mammography	Aspiration cytology	False negative	Sensitivity (%)
*	*			12	92·8
*			*	9	94·6
*		*		7	95·8
*	*	*		5	97·0
*	*		*	4	97·6
*		*	*	2	98·8
*	*	*	*	1	99·4

* Indicates the methods which are combined to calculate theoretical sensitivity

Relative sensitivity

In this study and previous studies from this centre, ultrasound mammography has a higher sensitivity for cancer than clinical examination, X-ray mammography or aspiration cytology. Furthermore, it is also more authoritative in its diagnosis, since 72·7 per cent of the true positive ultrasound results were +2 rather than +1, compared with 54·0 per cent for clinical examination, 63·5 per cent for X-ray mammography and 73·9 per cent for aspiration cytology.

Combined sensitivity

Table 2 presents the theoretical sensitivity for carcinoma for combinations of investigations. These figures are derived from the results of all 223 patients.

In the one patient in whom malignancy was not positively identified by any method, the lesion was thought to be a discrete plaque of benign breast change (scored −1). X-ray mammography was unhelpful because of density and the cytological specimen was inadequate.

Ultrasound mammography correctly identified three cases as malignant (+1 or +2) in which the other methods gave inconclusive (score 0) or benign (−1 or −2) results. Similarly, aspiration cytology correctly identified four carcinomas and X-ray mammography one carcinoma when the other methods gave scores of 0, −1 or −2.

False positive diagnosis of malignancy

Ultrasound and X-ray mammography each gave 15 false positive diagnoses of malignancy among the 57 patients who proved to have benign histology (a specificity of 73·7 per cent). Clinical examination produced nine false positives (specificity of 84·2 per cent). Aspiration cytology had no false positives (specificity 100 per cent).

In nine patients both ultrasound and X-ray mammography falsely diagnosed carcinoma. These false positives were due either to the overlap of the features of circumscribed carcinoma and fibro-adenoma on both ultrasound and X-ray mammography, or to the similarity of carcinoma and florid fibro-adenosis on ultrasound. This problem is discussed below.

The effect of ultrasound mammography on the scoring scheme

The scoring scheme provides an objective means of comparing the influence of either imaging method on treatment. It can be seen from *Table 3* that, if ultrasound were used rather than X-ray as the imaging method in the triple assessment, 15 more definitive procedures could have been undertaken without prior histological diagnosis. Thus frozen section or Trucut biopsy could have been avoided in 122 patients by using ultrasound as the imaging method and 107 by using X-ray. This represents a reduction of 25 per cent in the number of two-stage procedures—from 59 with X-ray to 44 with ultrasound.

Discussion

It has been argued that ultrasound mammography has a limited role in the diagnosis of breast carcinoma[10–12] because it is not a screening modality, being unable to detect the microcalcifications which signify a subclinical malignancy in some patients[13,14]. Indeed, in this study radiology detected one synchronous carcinoma in the contralateral breast because of microcalcification; sonography was used to evaluate this area but did not visualize any pathology. Therefore, it is clear that ultrasound is not to be regarded as a replacement for X-ray mammography, but rather as a complementary investigation.

Accurate diagnosis of malignancy without resorting to pre-operative biopsy such as frozen section enables the patient to have appropriate counselling before definitive surgery. Furthermore, valuable operating time is not wasted. It is for this purpose that triple assessment systems are employed in many centres; nevertheless, the emphasis must be on the avoidance of unnecessary ablative surgery. Hence in this study, the accuracy of ultrasound in improving reliable pre-operative diagnosis was investigated.

Table 3 illustrates that the incorporation of ultrasound mammography into a pre-operative diagnostic system can reduce the frozen section rate rather than if X-ray mammography were used. In real terms, the use of ultrasound in our scoring scheme allowed 73·5 per cent (122/166) of patients with carcinoma to have definitive treatment without prior biopsy, which compares with 64·5 per cent (107/166) using a standard system with X-ray as the imaging method.

Furthermore, the use of radiology alongside sonography would further increase the sensitivity of a pre-operative diagnostic scheme (*Table 2*) and would confer the benefits of screening.

The potential of ultrasound in this context is explained by various factors. In this centre, sonography is more sensitive for the diagnosis of carcinoma in the symptomatic breast than X-ray mammography[8,15] (*Table 1*), and this is borne out in other centres[16–18]. A few authors claim a sensitivity as high as 97 per cent[10] for X-ray mammography, although this is with 'state of the art' equipment and is higher than most other centres can achieve[19,20]. Furthermore, ultrasound has a higher 'relative sensitivity' than X-ray, so that it can diagnose malignancy with greater authority. Finally, ultrasound can image pathology which is obscured in the X-ray dense breast[15,21,22]. In this

Table 3 *Distribution of total scores (clinical examination + imaging + aspiration cytology): a comparison of radiology and ultrasonography*

	Malignant ($n = 166$)		Benign ($n = 57$)		
Total score	X-ray mammography	Ultrasound mammography	X-ray mammography	Ultrasound mammography	Treatment
−6 to −1	6	3	43	43	Excision biopsy
0 to +3	53	41	14	14	Frozen section/Trucut biopsy
+4 to +6	107	122	0	0	Definitive surgery

study, 16 patients who proved to have a carcinoma were not given a diagnosis of malignancy by X-ray mammography because density obscured the lesion. In each case ultrasound identified a focal mass and scored +2, +1 or 0.

The final treatment for each patient is influenced by each investigation. The investigations are therefore inter-related and complementary rather than competitive. For example, X-ray mammography has a screening ability whereas ultrasound mammography can image the radiologically dense breast.

Aspiration cytology has a negligible false positive rate[1,4,23,24] which is not matched by clinical examination, sonography or radiology. Thus ablative surgery must never be performed without cytological or histological confirmation of diagnosis. To illustrate this maxim, in this study, six masses were scored +1 by clinical examination, ultrasound mammography and X-ray mammography; cytology in each case was benign or inadequate. Histology revealed four fibroadenomas and two plaques of benign breast change. This overlap of the features of some fibro-adenomas and circumscribed carcinoma is clearly described in the literature[15]; for this reason, it is advised that any well-defined mass visualized by ultrasound should be excised and submitted for histology[10,25–27]. Furthermore, florid benign breast change can cast an acoustic shadow similar to that produced by a carcinoma[18,19,28]; this is another recognized cause of false positive diagnosis with ultrasound mammography.

We are at present investigating the use of ultrasound localization to increase the sensitivity of aspiration cytology due to unsatisfactory aspirates. In those few patients with unsatisfactory aspirates we perform Trucut biopsy to obtain definitive histological material.

In conclusion, the large turnover of patients in a busy breast clinic necessitates efficient and reliable diagnosis to avoid unnecessary surgery, to allow proper pre-operative counselling and to provide adequate screening. It is in this setting that the scoring scheme, the cytology service and the ultrasound facility were developed. When used as an adjunct to clinical examination, X-ray mammography and aspiration cytology, ultrasound can reduce operating time and costs and enable more specific information to be given to the patient before surgery.

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Relative merits of ultrasound and intravenous urography in the investigation of the urinary tract

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Three hundred and fifty adult patients referred for intravenous urography were entered into a prospective double blind trial comparing intravenous urography with real time ultrasound. The study was performed to clarify the relative merits of the two techniques. Our results show that ultrasound and a plain abdominal radiograph should be the examination of first choice in most circumstances. This is particularly so in vague abdominal pain and in recurrent urinary tract infections where intravenous urography can usually be omitted or used only as a secondary investigation for further evaluation of abnormal ultrasound findings. In acute renal colic, intravenous urography should be the primary investigation. In macroscopic haematuria, initial examination by ultrasound would reliably diagnose mass lesions, show whether the lesion is cystic or solid and assess possible spread. Normal ultrasound does not exclude haematuria due to ureteric lesions or bladder lesions and intravenous urography is recommended.

Keywords: Urinary tract, haematuria, abdominal pain, ultrasound, urograph

Real time ultrasound is widely available. Several authors have addressed themselves to the role of ultrasound in specific urological complaints$^{1-4}$; however, there is a lack of data on the role of ultrasound as the *initial* investigation of the urinary tract. Our study attempts to answer these questions and rationalize the selection of the appropriate examination in particular clinical circumstances.

Because ultrasound is safer and cheaper than intravenous urography considerable benefit could accrue from its use as the primary investigation.

Patients and methods

A sample of 350 adult patients took part in the trial (177 men, 173 women). All the patients referred for intravenous urography during normal working hours were included. The referral base was wide, ranging from urologists to general practitioners.

A real time ultrasound examination of the urinary tract was performed first by a radiologist (B.J. or D.J M.) using a 3·5 MHz sector scanner. The kidneys and bladder were imaged in multiple planes including longitudinal and transverse axes. If the bladder was not sufficiently full, the patient was rescanned during intravenous urography immediately before the postmicturition film. A report was prepared at the completion of the ultrasound examination.

An intravenous urogram was then performed by a different radiologist unaware of the ultrasound findings. The choice of contrast medium and film sequence was left to the individual concerned We normally use 50 ml sodium iothalamate (Conray 420) or equivalent and obtain films of the renal areas at 5 and 15 min, usually with abdominal compression, and further films of the bladder both before and after micturition. Tomography was performed when it was considered necessary. All the intravenous urograms were reported by one of the authors (D.R.N.), and he was not aware of the ultrasound report.

At the outset, routine preparation for intravenous urography involved fasting the patient before the examination Review of the first 100 cases revealed that the degree of dehydration could mask early pelvicalyceal distension on the ultrasound examination Previous studies[5] have shown that the quality of intravenous urography is not affected by lack of prior dehydration, and thus for the majority of the survey we asked our patients to drink normally and to attend with a full bladder.

To achieve direct comparison between ultrasound and intravenous urography each kidney and its collecting system was scored independently It is important to note that each kidney could score in more than one anatomical category i e. cyst, calculus, pelvicalyceal distension. Anatomical categories were used to allow direct comparison.

Clinical indications for requesting intravenous urography were also recorded so that the results for particular clinical indications could be compared. Four main categories were selected for closer comparison: acute renal colic (33 cases), recurrent urinary tract infections (42 cases), macroscopic haematuria (74 cases) and vague, non-specific abdominal and loin pain (88 cases).

Related or incidental findings outside the renal tract were also recorded.

Results

In the 350 patients examined 696 kidneys were assessed. One hundred and thirty eight patients had no abnormal findings on either examination.

Tables 1, 2 and *3* show the findings in the urinary tract.

The findings outside the urinary tract are shown in *Table 4*. *Tables 5* to *8* list the true positive findings in patients presenting

Table 1 *Findings in the kidneys*

	Intravenous urography only	Intravenous urography and ultrasound	Ultrasound only
Renal mass	0	6	1
Cyst	2	3	28
Calculi	17	16	11
Absent kidney	0	4	0

Values are the number of kidneys affected

Table 2 *Findings in the pelvicalyceal system*

	Intravenous urography only	Intravenous urography and ultrasound	Ultrasound only
Dilatation: Slight	5	19	6
Moderate	3	24	2
Severe	0	15	5
Pelvi-ureteric obstruction	2	3	0
Duplex system	9	4	1

Values are the numbers of systems affected. Pelvicalyceal dilatation was graded according to the criteria used by Lee *et al.*[6] and by Ellenborg *et al*[2]

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Table 3 *Findings in the bladder*

	Intravenous urography only	Intravenous urography and ultrasound	Ultrasound only
Bladder mass	3	7	5
Calculi	1	4	1
Enlarged prostate	2	25	7

Table 4 *Incidental findings on examination by ultrasound*

	Number of cases
Gallstones	5
Ovarian cyst	10
Ovarian cystadenoma	1
Pleural effusion	1
Aortic aneurysm	1

Table 5 *Recurrent urinary tract infections – 42 cases, 36 normal*

Positive findings	Number of cases
Renal cyst	1
Pelvicalyceal dilatation	2
Renal calculi	2
Bladder tumour	1
Bladder diverticulum	1
Prostatic enlargement	1

with particular clinical indications. The patients with renal colic are those with colicky pain, radiating from loin to groin and this group is considered separately from patients with less specific abdominal or loin pain.

Discussion

In children, real time ultrasound has largely replaced intravenous urography in most situations. The differing pathology found in adults means that there will always be a place for a number of intravenous urograms, but equally a proportion of the currently performed examinations could be reliably replaced by ultrasound.

A significant finding in this study was that in 138 cases (39 per cent), no abnormality was detected on either examination.

Our results confirm that ultrasound is superior in demonstrating *renal cysts*, and ultrasound has a recognized role in demonstrating the cystic nature of renal masses found at urography. Both examinations are equally good at diagnosing *renal masses*, and the two examinations have a complementary role—ultrasound to show the solid nature of the mass and urography to confirm a normally functioning contralateral kidney. The one case where a mass was diagnosed on ultrasound but not on intravenous urography, was due to focal renal hypertrophy. More importantly, no false negative cases were recorded.

We have not found ultrasound to be reliable at detecting *renal calculi*. Most renal calculi are radio-opaque and it is thought that the 11 cases of renal calculi suggested by ultrasound alone may have been due to acoustic reflections from blood vessels. Seventeen cases of radio-opaque renal calculi were not detected by ultrasound; none of the ureteric calculi was directly visualized by ultrasound, although they were seen on the plain abdominal radiographs.

Slight *pelvicalyceal dilatation* can be difficult to diagnose on ultrasound. However, if patients are dehydrated, dilatation due to partial obstruction could be missed. We identified three cases which were classified as showing moderate dilatation on intravenous urography and slight dilatation on ultrasound. On review of these cases, the original reports were considered correct. We believe adequate hydration is necessary to detect early pelvicalyceal dilatation and also allows examination of the bladder and pelvis by ultrasound. If it is thought that apparent pelvicalyceal distension may be because of bladder distension, the patient should be rescanned following micturition.

In cases of gross *hydronephrosis*, an intravenous urogram may only show a non-functioning kidney. Ultrasound in these cases is relatively simple and dilatation of the ureter is usually easily confirmed if it is present Ultrasound is not specific at diagnosing *pelviureteric obstruction*, but is sufficiently sensitive for further investigation to be instigated. In two of five cases, pelviureteric obstruction was not actually suggested by ultrasound, but moderate pelvicalyceal dilatation was reported. The ultrasound examination of all five cases would have prompted further investigation into the cause of pelvicalyceal dilatation.

Prostatic enlargement can be assessed clinically and the main reasons for requesting urography are to assess dilatation of the upper tracts and to estimate residual volume. Both of these aims can be achieved equally well by ultrasound.

Ultrasound detected several unsuspected abnormalities, some of which were significant in terms of the presenting symptoms, and which would not have been shown at urography.

Studies have shown that intravenous urography has little to offer patients presenting with *recurrent urinary tract infections*[1]. Most of these patients (36) had no abnormality and, if investigation is considered necessary at all, ultrasound and a plain film of the abdomen will detect most abnormalities Intravenous urography should be reserved for further evaluation of an abnormal ultrasound finding.

In patients presenting with *acute renal colic* there is a high probability of urinary tract calculi. It has been suggested by

Table 6 *Renal colic – 33 cases, 15 normal*

Positive findings	Number of cases
Pelvicalyceal dilatation	9
Renal calculi	5
Ureteric calculi	8
Renal cyst	2
Renal mass	1
Prostatic enlargement	1

Table 7 *Non-specific abdominal/loin pain – 88 cases, 67 normal*

Positive findings	Number of cases
Pelvicalyceal dilatation	14
Renal calculi	2
Ureteric calculi	4
Renal cyst	5
Prostatic enlargement	2

Table 8 *Macroscopic haematuria – 74 cases, 27 normal*

Positive findings	Number of cases
Pelvicalyceal dilatation	15
Renal calculi	7
Ureteric calculi	2
Renal cyst	11
Renal mass	3
Prostatic enlargement	14
Bladder tumour	9

some authors that ultrasound should be the first investigation in these patients[3,4]. Our experience is that ultrasound is unreliable in assessing possible renal or ureteric calculi. Although ultrasound will reliably demonstrate pelvicalyceal dilatation due to obstruction, a small number of patients will have ureteric calculi without proximal dilatation (two cases in this series). Patients presenting with acute renal colic require an unequivocal diagnosis, since if the urinary tract is not the source of the symptoms, an alternative diagnosis must be considered urgently for the severe symptoms.

For this reason, and because a possible ureteric calculus must be shown to be within the ureter, intravenous urography is reasonably the first investigation in these cases. Once the diagnosis is established, follow-up can be easily achieved with plain films and ultrasound—repeat intravenous urography should rarely be required.

In contrast, patients presenting with *nonspecific abdominal and loin pain* are much less likely to have a positive finding (67 cases normal in a group of 88 cases). These patients should be evaluated initially by ultrasound and a plain abdominal radiograph; if the urinary tract appears normal, the examination should be extended to include the liver, gallbladder, pancreas and pelvis.

In patients presenting with *macroscopic haematuria*, ultrasound and a plain film will detect most abnormalities, and assess potential spread in the case of tumours. However, if ultrasound is normal, intravenous urography should be performed as ureteric causes may not be detected by ultrasound. We wish to emphasize that neither intravenous urography nor ultrasound is sufficiently reliable to exclude bladder lesions and cystoscopy remains the examination of choice and should not be omitted.

The preceding paragraphs have attempted to rationalize the use of intravenous urography and ultrasound in some of the commoner clinical situations. Most imaging departments are now capable of providing a good ultrasound service. More radiologists and radiographers are being trained in this technique, and technical developments continue to make ultrasound both easier and more reliable. Ultrasound and a plain abdominal X-ray can safely be used as the primary investigation in most patients presenting with urological symptoms. The main weakness of ultrasound is in detecting calculi and possible ureteric pathology. For a correct diagnosis to be achieved and appropriate further investigation to be instigated, there must be a close rapport between clinician and radiologist. This is particularly true of ultrasound where greater reliance is placed on the latter's opinion.

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Intra-operative localization of bleeding small intestinal lesions

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We prospectively studied 12 patients to compare fibreoptic enteroscopy and methylene blue injection through superselectively prepositioned angiographic catheters in intra-operative localization of bleeding small intestinal lesions. Four patients were excluded because the lesions were easily detected by gross examination. Eight patients were subjected to study by these two methods. As methylene blue injection required a positive angiography, it was possible only in five patients. In two of these five patients, non-bleeding lesions were present outside the intestinal segments localized by this method. Enteroscopy was simple, accurate and reliable in seven patients. Complete enteroscopy was impossible in one patient with advanced lymphoma because the intestine and its mesentery were matted together. Fortunately, the bleeding ulcers were still within the reach of the endoscope. Enteroscopy localized bleeding small intestinal lesions more exactly than methylene blue injection so that the length of gut resection could be shorter. We, therefore, conclude that enteroscopy is the better intra-operative localization procedure.

Keywords: Intra-operative enteroscopy, methylene blue injection, bleeding small intestinal lesions

Bleeding small intestinal lesions are notoriously difficult to diagnose and localize[1]. Owing to the length and mobility of the small intestine, most of it is inaccessible to the ordinary endoscope and, unlike the stomach, the duodenum and the colon which are relatively fixed anatomically, pre-operative localization with barium studies, isotope scans and selective angiography will at best give a hint of the site of the bleeding lesion. Exact localization is impossible and the lesion has still to be found at operation[1,2].

There are many intra-operative methods of localizing small intestinal lesions[2]. Gross examination by palpation and transillumination is unreliable for small lesions, especially vascular lesions. During the time when pre-operative and intra-operative localizations were not readily available, laparotomy and gross examination yielded a diagnosis in only 30 per cent of patients with gastrointestinal bleeding of obscure origin[3]. Multiple enterotomies with eversion of mucosa or sigmoidoscopy are messy and increase the operative risks[1,2]. In the past, intra-operative mesenteric angiography[4], intra-operative mesenteric venous pressure and PaO_2 determinations[5] and the intra-operative Doppler ultrasound flow detector[6] were used for the localization of intestinal arteriovenous malformations (AVMs). These methods are cumbersome and time consuming[4,5], require extensive dissection[5], are unreliable for small lesions[4–6] and are unhelpful in the identification of bleeding lesions other than AVMs[5,6]. The best available methods for localization of bleeding small intestinal lesions nowadays are fibreoptic enteroscopy[1,2,7–13] and injection of methylene blue through prepositioned angiographic catheters[14]. As there are advantages and limitations in both procedures and there is no study in which they are compared, we decided to undertake a prospective study to ascertain the better procedure.

Material and methods

From 1985 to 1987, 12 patients with proven bleeding small intestinal lesions were admitted to our unit. They presented with gastrointestinal bleeding of obscure origin which is defined as a failure to localize the bleeding source after conventional investigations[2] These included at least one, and often more, emergency end- and side-view upper gastrointestinal endoscopies, barium meal, sigmoidoscopy, colonoscopy, and barium enema to exclude oesophagogastroduodenal and colorectal lesions All these patients had massive, continuous or recurrent bleeding.

A careful history, including a good family history of gastrointestinal bleeding and a history of drug intake, was routinely taken The facial stigmata of Peutz–Jeghers syndrome, blue rubber-bleb naevus syndrome[15] and skin telangiectasia of hereditary haemorrhagic telangiectasia[16] were specially looked for in the physical examination. Blood dyscrasia, clotting defects and other metabolic disorders were excluded by laboratory investigations. When conventional investigations failed to reveal the bleeding source, the patients were investigated with small bowel enema, ^{99m}Tc pertechnetate scan, ^{99m}Tc-labelled red blood cell scan and selective coeliac and mesenteric angiography[2]. As far as possible, we tried to localize the lesions before surgery During investigation, the patients were monitored closely and were managed actively with blood transfusions

If selective angiography demonstrated a bleeding small intestinal lesion, the angiographic catheter was advanced distally and a superselective angiography was carried out to delineate as short as possible a segment of gut containing the lesion. Patency of the catheter was maintained with intermittent syringe injection of heparinized saline and the patient was immediately transferred to the operating room.

All patients with gastrointestinal bleeding of obscure origin were operated in the lithotomy position with the abdomen and perineum draped so that the intra-operative enteroscopy, if required, could be performed[1]. At laparotomy, a careful search of the bleeding lesion by palpation and transillumination against a strong light was performed from the duodenojejunal flexure down to the ileocaecal valve. Care was taken not to displace the angiographic catheter, if present, during this

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examination. If a bleeding Meckel's diverticulum was found, no further intra-operative localization procedure was performed. For patients with a prepositioned angiographic catheter, 1 ml of methylene blue was injected through the catheter and the small intestinal segment stained blue was marked proximally and distally with silk stitches. Intra-operative enteroscopy was then performed. Whole gut irrigation was either done pre-operatively in elective operations or intra-operatively in emergency operations[17]. Our technique of enteroscopy has been reported[1] In brief, we used an Olympus TCF-2L2 colonoscope (Olympus Optical Company Ltd, Japan) which has a working length of 1·6 m. The scope was inserted by an endoscopist through the anus and/or the mouth. The tip of the endoscope was guided up the colon or down the duodenum into the small intestine by the abdominal surgeon who telescoped the small bowel on to the endoscope. After full introduction of the endoscope into the intestine, the endoscope was gradually withdrawn. In segments of 10 cm, the lumen was examined by the endoscopist and the external surface of the transilluminated gut inspected by the abdominal surgeon. The sites of bleeding lesions were marked with silk stitches on the serosal surface. The gut was decompressed when the endoscope was withdrawn so that closure of the abdomen presented no problem.

Results

Seven male and five female patients had bleeding small intestinal lesions. Their ages ranged from 3 to 71 years (mean ± s.d. = 43 7 ± 24·3 years). Recurrent bleeding occurred in ten patients; the last attack before diagnosis and surgery was massive in two patients, slowly continuous in three patients and stopped completely in five patients. Two patients presented with massive bleeding in the first attack. The median time from the first bleed to diagnosis was 1·6 years (range, 1 day to 5 years). Pre-operative blood transfusion ranged from 1·5 to 16 litres (mean ± s.d. = 5·9 ± 3·8 litres).

Four patients with bleeding Meckel's diverticula presented no difficulty in pre-operative diagnosis or intra-operative localization and are not discussed further.

A comparison of the intra-operative localization procedures for the other eight patients by gross examination, injection of methylene blue through prepositioned angiographic catheters and enteroscopy is listed in *Table 1*. Gross examination was unreliable for small and superficial lesions. Injection of methylene blue was possible in five patients. However, in two of them, who had lymphoma with multiple small intestinal ulcers, several non-bleeding ulcers were present outside the intestinal segments that were stained blue. Intra-operative enteroscopy was easy, accurate and reliable in seven patients. Complete enteroscopy, however, was impossible in a patient with advanced lymphoma because the gut and its mesentery were matted together. Fortunately, the bleeding ulcers were within the reach of the endoscope so that the extent of gut resection could still be determined. Enteroscopy localized bleeding small intestinal lesions more exactly than methylene blue injection so that the length of gut resection could be shorter. We, therefore, conclude that enteroscopy is the better intra-operative localization procedure.

Two patients died postoperatively (17 per cent): one patient with polyarteritis nodosa died 15 days after operation because of uncontrolled chest infection, and another patient with lymphoma died 6 weeks after operation because of advanced disease.

The median follow-up for the ten patients that survived the operation was 16 months; there were no recurrences of gastrointestinal bleeding in these patients.

Discussion

Bleeding small intestinal lesions are notoriously difficult to diagnose pre-operatively and to localize intra-operatively[1]. Gross examination by palpation and transillumination is unreliable and it often fails to detect the bleeding lesions[1–3,7]. This is not surprising since it is now recognized that about 40 per cent of cases of chronic obscure gastrointestinal bleeding are due to AVMs[7] which are usually not readily visible or palpable at operation[18]. Occasionally, in patients with more than one possible bleeding lesion found intra-operatively, the exact bleeding site is uncertain unless bleeding has been directly observed either angiographically or endoscopically.

Injection of methylene blue requires a positive pre-operative selective angiogram[14,19]. For angiography to demonstrate a bleeding lesion, there must be active bleeding at a rate above 0·5 ml/min at the time of injection of the contrast material[20]. Gastrointestinal bleeding of obscure origin is generally an intermittent, highly variable occurrence and patients with normal angiography may still have actively bleeding lesions[7,21]. Some lesions like AVMs, haemangiomas, leiomyomas and Meckel's diverticula with ectopic gastric mucosa may occasionally be demonstrated in angiography in the absence of bleeding[18]. For unknown reasons, some intestinal vascular lesions may not be apparent on one examination and yet be obvious on another[22].

Table 1 *Details of patients with bleeding small intestinal lesions*

		Intra-operative procedures		
Pathology	Site of lesion	Gross examination	Injection of methylene blue	Enteroscopy
AVM	Jejunum	Not found	Localized to 30 cm of jejunum	Exact localization of lesion
AVM	Jejunum	Not found	Localized to 30 cm of jejunum	Exact localization of lesion
Non-specific ulcer (steroid-induced)	Jejunum	Not found	Localized to 10 cm of jejunum just distal to duodenojejunal flexure	Eact localization of bleeding ulcer
Lymphoma	Ileum	Multiple ulcers, bleeding site unknown	Segment of ileum, 40 cm, containing bleeding ulcers localized, non-bleeding ulcers outside localized gut segment	Bleeding and non-bleeding ulcers seen; this helped in deciding length of gut resection
Lymphoma	Jejunum and ileum	Small gut and its mesentery matted together, multiple ulcers found, bleeding site unknown	Segment of ileum, 45 cm, containing bleeding ulcers localized; non-bleeding ulcers outside localized gut segment	Complete enteroscopy impossible because gut and mesentery matted together; bleeding and non-bleeding ulcers were seen
Lymphoma	Ileum	Two ulcers found	Not possible because of negative angiography	Three ulcers close to one another seen
Jejunal diverticulum	Jejunum	Diverticulum found ?? bleeding	Not possible because of negative angiography	Bleeding from diverticulum seen
Polyarteritis nodosa	Jejunum	Spastic segment of jejunum	Not possible because of negative angiography	Punctate bleeding in spastic segment of jejunum seen

AVM, intestinal arteriovenous malformation

Athanasoulis and his associates reported an ingenious intraoperative localization procedure by injecting methylene blue through a superselectively prepositioned angiographic catheter[14]. They used two co-axial catheters and advanced the inner catheter, as distally as desired in the jejunal artery supplying the lesion, under fluoroscopy with image intensification and magnification. This was done electively in a second arterial catheterization just before surgery. We modified their techniques by performing a superselective angiography using a single preshaped catheter and advanced it as distally as possible in a single stage. This modification allows immediate surgery to be performed to stop bleeding, avoids a second arterial catheterization and eliminates the possibility that the lesion may not show up in the second angiogram because of slowing down of the bleeding.

Fibreoptic enteroscopy has been done with good results[1,2,7–13]. Because of the rarity of bleeding small intestinal lesions, most experiences on enteroscopy are based on reports of one to two cases[7–12], with only occasional reports of slightly larger series of patients[1,2,13]. Using the colonoscope, which is the longest and easily available fibreoptic instrument, complete visualization of the entire small intestine is possible[1]. It has the advantages of being simple, accurate and reliable. Lesions are exactly localized and are confirmed to be bleeding under direct vision. Moreover, by a complete examination of the whole intestine, the surgeon can decide on the extent of gut resection with a greater degree of confidence and he can be certain that no bleeding lesions are left undetected. The only limitation of enteroscopy is technical. In patients with advanced malignancies[2], and in patients with dense adhesions due to repeated operations[12], complete enteroscopy may, on rare occasions, be impossible. There may be concern that small vascular lesions are not visible endoscopically as these lesions are not visible in the resected specimens unless injected with barium gelatine[23] or silicone rubber[24]. It would seem logical that if a lesion causes bleeding, a mucosal defect should be present[25] and mucosal ulcerations are common in AVMs[26]. In living patients, vascular lesions are bright red and are easily visible through an endoscope[6,27]. Transillumination by strong light from the endoscope in the gut lumen through the wall increases the chance of detection of these vascular lesions[28]. We have been able to identify very small AVMs by enteroscopy in this study as well as in previous studies[1,2].

Based on our results, fibreoptic enteroscopy is the best intraoperative localization procedure and it should be freely used. In patients with a positive selective angiogram, however, we still recommend a superselective angiography and to leave the angiographic catheter *in situ*. This will give an additional assurance that the bleeding lesion can be localized by injection of methylene blue on the rare occasions when enteroscopy is technically impossible.

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Venous mesenteric infarction: a particular entity

Ninety-eight patients with documented mesenteric infarction during a 19-year period were reviewed. In 13 patients infarction was due to a mesenteric venous thrombosis (MVT). Patients with MVT distinguished themselves from those having another aetiology by: (1) longer history of pain before admission (median 8 days, $P<0{\cdot}0001$*); (2) typical appearance of the bowel at laparotomy (10/13); (3) a localized segment of ischaemic jejunum or ileum of less than 120 cm in length (12/13) allowing better operability at the first laparotomy* ($P=0{\cdot}006$)*. In hospital the mortality was lower for venous mesenteric infarction (5/13, 38 per cent) than for mesenteric infarction of other aetiologies (70/85, 82 per cent)* ($P=0{\cdot}002$)*. Patients with primary venous mesenteric infarction showed a better survival rate (one death in eight patients) than patients with associated diseases such as liver cirrhosis, sepsis or previous operation who had a poor prognosis with a mortality comparable to other aetiologies of acute bowel ischaemia (four deaths in five patients). Since the high recurrence rate of this disease in the early postoperative period was due to residual venous thrombosis and to a hypercoagulable state, a wide bowel resection is recommended followed by early and long-term anticoagulation. Thrombectomy is probably inefficient since it removes only centrally located thrombi and leaves peripheral occlusion, which is responsible for the recurrence.*

Keywords: Venous mesenteric infarction, mesenteric venous thrombosis, portal thrombosis, anticoagulation

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Mesenteric infarction results from a variety of causes, each having its own characteristics[1]. Occlusion of the superior mesenteric artery (SMA) is responsible for 50–75 per cent of acute mesenteric ischaemia, and infarctions without vessel occlusion are found in 15–40 per cent[1–5]. Both have a poor prognosis with a mortality generally exceeding 80 per cent. Venous occlusion is the cause of mesenteric infarction in less than 20 per cent and has a better prognosis[5–7].

This retrospective study was undertaken to point out the clinical syndrome, the operative findings and the postoperative course of patients with mesenteric infarction of a venous aetiology and to compare it with mesenteric infarction of other aetiologies. All cases of mesenteric infarction hospitalized in our department of surgery since 1968 have been reviewed.

Patients and methods

Between January 1968 and April 1987, 98 consecutive patients have been admitted to our hospital with a mesenteric infarction. The diagnosis was ascertained in all cases on the basis of angiography ($n=28$), laparotomy ($n=83$) and/or autopsy ($n=67$)

In 13 of these patients (13 per cent) bowel infarction was caused by a mesenteric venous thrombosis (MVT) in the absence of arterial occlusion. Eight presented no predisposing factors for venous thrombosis whereas in five patients the MVT was associated with liver cirrhosis ($n=2$), with previous abdominal operation (an appendicectomy and a cholecystectomy) ($n=2$) and with diffuse peritonitis following a perforated sigmoid diverticulum ($n=1$). On admission, the youngest patient with MVT (43 years) presented with an antithrombin (AT) III deficiency of less than 40 per cent of the normal value Serial controls of AT III showed a normalization of the AT III after 2 months, suggesting a non-congenital deficiency. A family study revealed no other AT III deficiency. This patient was therefore considered to have a primary venous mesenteric infarction.

Other aetiologies of bowel infarction included an embolus of the SMA in 39 patients (40 per cent), a thrombosis of the SMA in 18 patients (18 per cent) while in another patient the obstruction of the SMA could not be identified either as an embolus or as thrombosis. No mesenteric vascular occlusions were noted in 19 patients (19 per cent) and 8 patients had a rare aetiology including a thrombosis of the inferior mesenteric artery with an infarction localized on the left colon ($n=3$), an obstructive infiltration of the SMA by a bowel carcinoid ($n=1$), peripheral arterial occlusion caused by small cholesterol emboli in the sigmoid colon ($n=1$), multiple arterial and venous thrombosis in a patient receiving oestrogen therapy ($n=1$) and disseminated intravascular coagulation with massive bowel infarction ($n=2$)

Characteristics of patients with venous mesenteric infarction or mesenteric infarction of other aetiologies were compared using the χ^2 test on contingency tables with Yates' correction or Fisher's exact test.

Results

The 13 patients with documented venous mesenteric infarction comprised 8 men and 5 women. Their median age was 68·5 (range 43–79) years. The 85 patients with infarction of other aetiologies had a median age of 70·2 (range 27–89) years and comprised 47 women and 38 men. Patients with primary venous thrombosis and non-occlusive infarction were younger (median age 66·5 and 63 years respectively) than those with venous thrombosis associated with predisposing factors or with SMA occlusion (median age 77·5 and 74 years respectively, $P<0{\cdot}005$, Wilcoxon–Mann–Whitney test[8,9]).

Pre-operative findings (Figure 1)

All 98 patients in our series complained of abdominal pain. It is noteworthy that the median duration of pain before admission in patients with MVT was significantly longer (median 8 days, range 2 days to 6 weeks) than that in patients with infarction of other aetiologies (median 2 days, range 2 hours to 11 days) ($P=0{\cdot}0001$, Wilcoxon–Mann–Whitney test). Furthermore, all 13 patients with MVT described the pain as intermittent and generally bearable at the beginning. Duration of pain was particularly long in three patients who had predisposing factors (3, 4, and 6 weeks) and also presented with mesentericoportal thrombosis. Previous episodes of either deep vein thrombosis of the extremities or of pulmonary emboli were found in 7 of the 13

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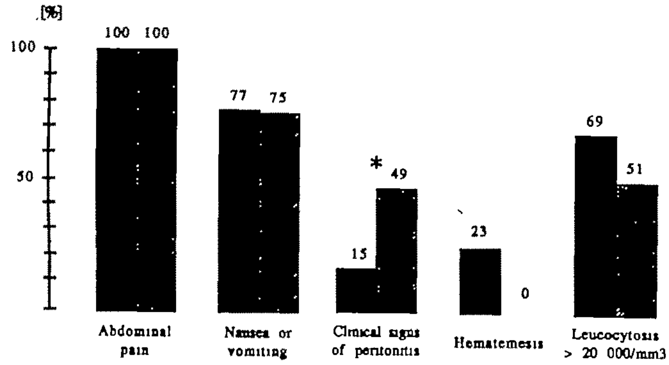

Figure 1 *Comparative frequency of criteria noted on admission in patients with mesenteric infarction from a venous aetiology and from other aetiologies. Values are percentages and refer to the total of 13 patients and 85 patients, respectively. *Difference statistically significant* ($\chi^2 = 3{\cdot}99$, $P < 0{\cdot}05$). ■, *Venous mesenteric infarction* (n = *13*); ▨, *mesenteric infarction of other aetiologies* (n = *85*)

patients with MVT. Five of them had no predisposing factors. Nausea or vomiting was found in about 75 per cent of patients with mesenteric infarction, irrespective of the aetiology. Clinical signs of peritonitis (tenderness, rebound pain and guarding) were noted less frequently in patients with MVT than in those with mesenteric infarction of other aetiologies ($P < 0{\cdot}05$). Three of the thirteen patients with a venous mesenteric infarction had acute upper abdominal bleeding during the first 24 h of hospitalization. All three patients had a pre-operative gastroduodenoscopy, which could not identify the source of the bleeding. Upper abdominal bleeding was never found in patients with mesenteric infarction of other aetiologies. A leucocytosis above 20×10^9/l was noted more frequently in patients with venous mesenteric infarction; however, this difference was not significant.

In only 1 of the 13 patients with venous mesenteric infarction the first plain X-ray of the abdomen after admission showed a typical thickening of the intestinal wall, valvulae conniventes and thumbprinting images. In the other 12 patients, however, abdominal X-ray showed only uncharacteristic images that were compatible with any diagnosis of acute abdomen.

Selective and pre-operative arteriography has been used in our institution on a systematic basis only recently. So far it has been used for two patients with MVT. In both these patients a normal arterial tree and indirect signs such as arterial spasm were found and in one delayed venous filling was described.

Pre-operative CT scans were used in two patients with primary MVT, but did not detect any thrombosis.

Operative findings and treatment

All 13 patients were operated on within the first 3 days following admission. Twelve of them could be treated, an operability rate of 92 per cent. This is a much higher operability rate than that found in the 85 patients with non-venous infarction (54 per cent, 46/85; $P = 0{\cdot}006$). In 10 of the 13 patients with venous infarction a serosanguineous peritoneal fluid was noted and the macroscopic appearance of the intestine has been described as dark-bluish bowel, thickened wall and mesentery, and well-pulsating arteries. In the three remaining patients descriptive reports were inconclusive. According to the histological investigations the extent of bowel infarction was less than 120 cm in 12 of the 13 patients. In one patient with associated liver cirrhosis the infarction was judged to be too extensive for resection (> 2·5 m). This patient was treated by supportive care only. In the other 12 patients bowel damage was localized to the proximal jejunum ($n = 1$), middle jejunum ($n = 8$), ileum ($n = 2$) and the ileocaecal area ($n = 1$). According to the histological findings, bowel was resected between 3 and 7 cm away from the infarcted segment. No venous thrombectomy was carried out.

All 12 patients treated by resection received intra- and postoperative antithrombotic prophylaxis. Ten patients received intravenous dextran 40 or 70 (50 g/day started on the day of operation and perfused for 3–5 days) and five of these patients also received low-dose subcutaneous heparin (5000–15 000 units/day). The other two patients were put on intravenous heparin in therapeutic doses (i.e. AT-time > 2 min). All patients received long-term anticoagulation with coumarin (over 4 months) in the later postoperative course.

Postoperative course

Hospital mortality was 38 per cent (5/13) for venous mesenteric infarction compared with 82 per cent for other infarctions (70/85) ($P = 0{\cdot}002$). This relatively favourable prognosis of venous infarction was limited to patients without associated diseases. Only one of the eight patients with primary MVT died. Of the five patients with associated diseases four died within 22 days following the operation: three from multi-organ failure and one from a diffuse recurrent infarction. In addition, five of the eight patients with primary MVT developed recurrent bowel ischaemia within 16 days after surgery (median 8 days, range 2–21 days) and one died. In these six recurrences, involved bowel was always limited to the 10 cm adjacent to the anastomosis. Four of six recurrences were treated successfully by a second resection. Interestingly, in four of the six patients with recurrent infarction the histological reports mentioned the presence of thrombi at the resection site and in what appeared to be normal bowel.

Eight of the thirteen patients left the hospital and three died subsequently. The cause of death could be ascertained in all cases and was not related to an ischaemic bowel syndrome. Five are still alive; an interview was possible in four at intervals of 6 months to 13 years after their operation. Three of these four patients had no abdominal symptoms. One had an hyperoxaluria with oxalate stones without fat malabsorption.

Discussion

Mesenteric infarction resulting from a MVT is undoubtedly a distinct entity to be distinguished from other causes of mesenteric infarction[6,7]. It represents less than 20 per cent of all bowel infarctions and has a relatively good prognosis. Possibly a large proportion of MVT is silent or resolves spontaneously. Therefore, the incidence of MVT without severe or with reversible bowel damage remains unknown.

Venous mesenteric infarction is rarely diagnosed pre-operatively since few clinicians are familiar with the disease. As in all patients with acute bowel ischaemia, abdominal pain is the commonest first complaint. Interestingly, the duration and type of pain prior to admission are characteristic. Patients in our series complained of an average duration of pain of about 8 days before admission and in most cases described the pain as intermittent and—at least at the beginning—relatively bearable. This long history of pain has been mentioned by several authors[10–13]. Kirschner[10] in 1955 noted that more than 65 per cent of patients with MVT had abdominal complaints of more than 3 days duration and Mathews and White[11] found that pain had commonly been present for 5 days to 1 month before admission. In a more recent report of patients with primary venous mesenteric infarction[12] the average duration of pain before admission was 14 days. Intestinal damage occurs only when the vasa recta and intramural vessels are occluded[7,14]. Three of our patients with venous mesenteric infarction associated with predisposing factors and portal thrombosis described a particularly long painful prodrome. It has been suggested that in MVT associated with predisposing factors, the thrombi start generally in the portal vein and, through centrifugal propagation, reach the intestine, gradually inducing infarction[2]. In support of this concept, a post-mortem study[15] showed that portal clots were always older than the thrombi in the mesenteric veins. Therefore, it is probable that the more central the thrombus the longer is the prodrome.

Previous episodes of either deep vein thrombosis of the extremities or of lung emboli were found in five of the eight patients with primary venous mesenteric infarction suggesting a hypercoagulable state. Others[11] have reported a rate of 32 per cent for previous venous thrombosis.

On clinical work-up only peritonitis was noted significantly less frequently in the venous infarction group than in the group with other aetiologies, suggesting less advanced bowel damage in the first group. Conversely, leucocytosis was slightly more elevated in patients with the venous aetiology. According to Ottinger[16], the degree of leucocytosis follows the extent of bowel ischaemia and the duration of pain.

Acute upper gastrointestinal bleeding with abdominal pain and a normal endoscopic investigation could suggest the diagnosis of venous mesenteric infarction. In our series, haematemesis was never noted with mesenteric infarction of other aetiologies. Case reports of venous mesenteric infarction presenting as upper gastrointestinal bleeding have occasionally been published[17,18].

The plain abdominal X-ray is usually of no help in recognizing mesenteric infarction, particularly that with a venous aetiology. Typical bowel wall thickening, mucosal irregularity and thumb-printing images (focal haemorrhage)[6,7,19,20] were retrospectively found in only 1 of our 13 patients.

Pre-operative selective arteriography of the SMA has proved useful when mesenteric infarction is suspected[16,21–23]. It is now being used routinely for this indication at our institution[5]. Occlusions of the SMA are well recognized and angiographic findings permit definition of the site and type of arterial occlusion in most situations, thus allowing expedient revascularization according to the nature of the obstructive process[5,16,22,23]. In venous mesenteric infarction, besides lacking evidence of venous mesenteric drainage in the late phase, some indirect signs have been described with arteriography: namely reflux of contrast medium into the aorta, intense spasm of the SMA, prolonged opacification of the thickened bowel wall and border blush to the affected bowel segment[6,7,19–22]. In two of our patients with venous mesenteric infarction pre-operative arteriography findings showed some of these indirect signs and excluded an obstructive process in the SMA. However, arteriography findings did not allow a differentiation between a MVT and a non-occlusive infarction.

CT scanning has been reported recently as particularly accurate in detecting portal thrombosis[24] and could be useful for the diagnosis of MVT. In two of our patients with primary MVT pre-operative CT findings were negative.

At laparotomy the macroscopic appearance of the infarcted bowel suggests a venous aetiology. Serosanguineous peritoneal fluid is usually present. Involved bowel is dark red or blue-black, and oedematous. The bowel wall is infiltrated with blood, the mesentery is thickened and arteries pulsate[6,7,25,26]. The transition zone between normal and infarcted bowel is usually gradual[13,27]. In our study, typical venous infarction was described in 10 of the 13 patients.

As noted by others[6,7] the prognosis of venous infarction is related to the patient's age, the timing of surgical intervention and the associated diseases. When associated with liver cirrhosis, sepsis, previous operations or trauma the mortality is high and equals that of other aetiologies. When, however, mesenteric thrombosis is idiopathic[5,25–29], associated with AT III deficiency[30,31] or other subtle coagulopathies[32–34], the clinical course of the disease is commonly favourable after surgery and early anticoagulation. In some cases of familial AT III deficiency, danazol (a derivative of 17 α-ethynyl testosterone) has been proposed as an alternative to long-term anticoagulation. Its mechanism of action in increasing AT III level remains unknown[35]. In the youngest patient of our series AT III deficiency was transitory and not found in other members of his family. Therefore this deficiency has been interpreted as a consequence of the acute illness and not as the cause of the MVT. In such cases of secondary AT III deficiency, effective anticoagulation is indicated. Transient AT III deficiency has also been associated with oral contraceptives[36] and with anticoagulant therapy such as heparin[37] and has been shown to follow splenectomy[38].

Recently, we have reported a high recurrence rate of postoperative bowel ischaemia despite early treatment in all aetiologies of mesenteric infarction[5]. These recurrences were thought to be partly due to persistent arterial spasm. In venous mesenteric infarction we found a recurrence rate of almost 50 per cent for both primary and secondary venous occlusion despite early antithrombotic prophylaxis. These recurrences characteristically involved the 10 cm adjacent to the end-to-end anastomosis. Possibly, the extent of the lesion was misjudged and together with persistent arterial spasm contributed to the recurrence. A review by Jona *et al.*[39] showed that in 60 per cent of cases recurrence occurred at the site of the anastomosis, often causing anastomotic dehiscence. Consequently resection should include 15 cm of macroscopically normal bowel. Immediate antithrombotic prophylaxis with heparin or dextran, later substituted by coumarin, is indicated. Successful thrombectomy is exceptional[40,41]. Thrombectomy removes only thrombi localized in large venous trunks and leaves the obstruction in small veins in the vicinity of the bowel, causing ischaemia. In animal experiments, a residual intense arterial spasm has been found after removal of the venous occlusion[42]. Therefore any mechanical attempt at revascularization of larger veins by thrombectomy is not recommended.

In conclusion, MVT is a particular entity with a relatively good prognosis if the postoperative course is not compromised by severe disease. Previous thrombophlebitis of the extremities or lung emboli and a long history of abdominal pain suggest a venous aetiology. Pre-operative arteriography is helpful in excluding the occlusive aetiologies of the SMA. Beneficial effects of selective perfusion of vasodilators into the SMA in order to suppress arterial spasm remain to be demonstrated in MVT[5]. Laparotomy is indicated immediately after arteriography and resection lines should be away from the lesion. A revascularization technique is useless and anticoagulation has to be initiated without delay. A second look should be planned if bowel vitality remains doubtful. However, there is no good evidence that a routine second look in elderly patients or in the presence of severe associated diseases is advantageous.

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Angiodysplasia of the colon: endoscopic diagnosis and treatment

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Of 34 patients with massive lower intestinal bleeding, 17 (11 men and 6 women, age range 33–85 years; mean 64·8 years) were diagnosed as having angiodysplasia of the colon. The diagnosis was made by colonoscopy and the lesions were treated successfully by fulguration in 13 (86·6 per cent) of 15 patients. Two of the 17 patients underwent surgical resection of the involved intestinal segment. One patient still has sporadic intestinal haemorrhage, and another patient died from bleeding of the left colon after blind right colectomy. The remaining 13 patients have had no further bleeding in the 1–7 years following colonoscopic fulguration. Colonoscopy is a useful method of diagnosing angiodysplasia of the colon and affords the possibility of treatment.

Keywords: Angiodysplasia, fibreoptic endoscopy, fulguration

Arteriography has been used to diagnose the cause of active and non-active bleeding of the lower gastrointestinal tract, and since its advent[1], the percentage of undiagnosed cases of intestinal haemorrhage has been dramatically reduced. Angiodysplasia, a degenerative process of ageing[2], has been recognized as a frequent cause of lower intestinal bleeding in the elderly[3–6]. While there have been numerous cases in which angiodysplasia has been successfully diagnosed by selective mesenteric angiography[3–5,7–9], we have employed colonoscopy to diagnose those cases of massive intestinal bleeding caused by vascular lesions. This paper presents our experience with colonoscopy in this context.

Patients and methods

Between July 1978 and September 1986, 34 patients (18 men and 16 women, age range 17–85 years; mean 63·7 years) with massive lower intestinal bleeding underwent one or more colonoscopic examinations (Olympus CFMB 3R or CFLB 3R) in the Digestive Endoscopy Section of the University Hospital School of Medicine, Ribeirão Preto, São Paulo, Brazil. The examination was performed at the time of haemorrhage in five patients and after bleeding appeared to have stopped in 29 patients In those in whom the bleeding had stopped, preparation for colonoscopy consisted of oral administration of 100 dl 10 per cent mannitol 4 hours before examination. Of the 34 patients, 17 were diagnosed as having angiodysplasia of the colon (*Table 1*). The remaining patients proved to have the lesions listed in *Table 2*, although in two patients no lesion could be found.

Before colonoscopy almost all of these patients had been evaluated by nasogastric intubation, oesophagogastroduodenoscopy, barium meal examination and/or barium enema to attempt to define the source of haemorrhage but without success. Only two patients underwent selective mesenteric angiography.

Results and treatment of patients with angiodysplasia

Seventeen of the 34 patients (50 per cent) were shown to have 27 angiodysplastic lesions, 26 in the colon and rectum and one in the ileum (*Figure 1*). These patients (11 men and 6 women) were aged between 33 and 85 years (mean 64·8 years) (*Table 1*). Five patients were seen during their first episode of bleeding and were examined while the haemorrhage was continuing. Twelve patients who had more than two episodes of bleeding needed transfusions ranging in amount from 3 to 6 units of blood. In this series, most lesions were located in the right colon; however eight patients had nine lesions distal to the hepatic flexure (*Figure 1*).

Treatment consisted of 30 fulgurations applied to 27 lesions

Table 1 *Details of patients in whom massive intestinal bleeding was caused by angiodysplasia*

No.	Sex	Age	Site of lesion	Past or present associated lesion	Treatment	Follow-up*
01	Female	44	Descending	Carcinoma of colon	Fulguration	No re-bleeding
02		51	Caecum		Excision	Healed
03		52	Caecum sigmoid		Fulguration	No re-bleeding
04		62	Ileum caecum		Excision	Healed
05		65	Rectum		Fulguration	No re-bleeding
06		85	Caecum ascending		Fulguration	No re-bleeding
07	Male	33	Descending sigmoid		Fulguration	No re-bleeding
08		60	Caecum		Fulguration	No-rebleeding
09		62	Caecum		Fulguration	No re-bleeding
10		67	Descending		Fulguration	No re-bleeding
11		69	Caecum ascending transverse	Acquired megacolon, Chagas' disease	Fulguration	Unsuccessful
12		70	Caecum	Polyp	Fulguration polypectomy	No re-bleeding
13		71	Hepatic flexure	Diverticular disease	Fulguration	No re-bleeding
14		73	Ascending transverse	Diverticular disease	Fulguration	No re-bleeding
15		77	Caecum ascending	Diverticular disease	Fulguration	Unsuccessful
16		80	Caecum ascending transverse	Portal hypertension	Fulguration	No re-bleeding
17		81	Caecum		Fulguration	No re-bleeding

* From one to 7 years

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Table 2 *Details of patients in whom lesions other than angiodysplasia were a possible source of massive intestinal bleeding*

No.	Sex	Age	Endoscopic diagnosis	Treatment	Follow-up*
18	Female	17	Rectal ulcer	Medical**	Healed
19		38	Ileocaecal ulcer	Excision	Healed
20		45	Ileal ulcer	Excision	Death
21		50	Polyp	Polypectomy	Healed
22		60	Diverticular disease	Medical	No re-bleeding
23		75	Diverticular disease	Medical	No re-bleeding
24		79	Diverticular disease	Medical	No re-bleeding
25		81	Diverticular disease	Medical	No re-bleeding
26		82	Carcinoma	Colectomy	—
27		84	Diverticular disease	Medical	No re-bleeding
28	Male	55	Diverticular disease	Medical	No re-bleeding
29		57	'Normal'	Medical	No re-bleeding
30		65	Diverticular disease	Medical	No re-bleeding
31		68	'Normal'	Medical	No re-bleeding
32		68	Diverticular disease	Medical	No re-bleeding
33		70	Diverticular disease	Medical	No re-bleeding
34		71	Diverticular disease	Medical	No re-bleeding

* From one to 7 years; ** Medical, blood replacement

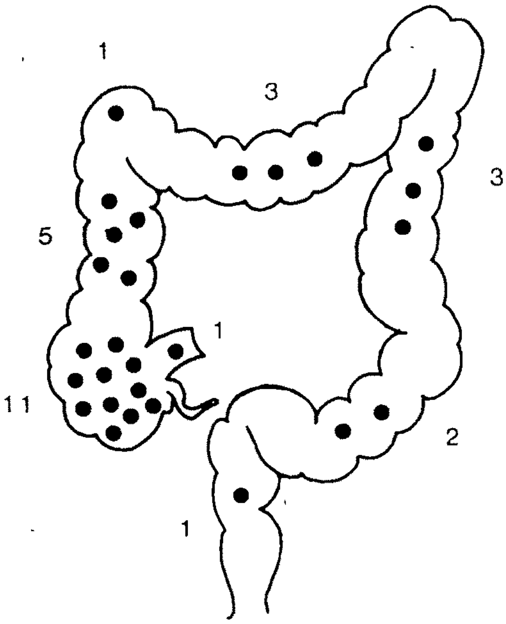

Figure 1 *Distribution of lesions in various parts of colon. Numbers indicate frequency*

in 15 patients, while two patients underwent resection of the intestine involving the lesion. One of the resected patients was a 51-year-old woman, the first of this series, and the other was a 62-year-old woman who was found to have angiodysplasia in the caecum and in the ileum. This patient was submitted to selective mesenteric arteriography which showed the lesion in the ileum. One of the patients having fulguration, a 69-year-old man, had a normal mesenteric angiogram. He underwent two colonoscopies. In the first, several angiodysplastic lesions were seen in the right and transverse colon and all were fulgurated. In the second colonoscopy, no lesion was found. However, one year later he re-bled and underwent blind right colectomy in another hospital, where he died 2 weeks later from bleeding from the left colon. Another fulgurated patient, a 77-year-old man, who underwent two colonoscopies for fulguration, still has sporadic intestinal haemorrhage, although angiodysplasia was not seen at the third colonoscopy. Thus, endoscopic fulguration was successful in 13 patients (86·6 per cent) in that none of them re-bled within a 1–7-year follow-up period.

Discussion

Massive intestinal bleeding remains a difficult clinical problem. For a long time, diverticular disease of the colon was accepted as the major colonic cause of massive rectal bleeding, so much so that in those patients with confirmed diverticula, the diverticula were considered to be the most likely cause of bleeding[10–14]. However, histological proof of diverticular haemorrhage was not always demonstrated[15]. Furthermore, the success of right-sided 'blind' colectomy in the treatment of massive colonic bleeding[10], the predilection of angiodysplasia for the right colon[16], the arteriographic demonstration of arteriovenous malformation of the caecum[11,17] and reports of arteriographic detection of the source of gastrointestinal bleeding[1], led to angiodysplasia being regarded as the main potential cause of massive lower intestinal bleeding.

The first report of a vascular lesion of the gastrointestinal tract was published in 1839[18]. Gentry *et al.*[19] in their review from the Mayo Clinic mentioned it as an entity and during the past 15 years more than 150 cases of vascular abnormalities, named angiodysplasia of the colon, have been reported[2–9,11,15,20–22]. Angiography has been used increasingly as a method of diagnosis and as a means of demonstrating the site of lower gastrointestinal bleeding[1,5,8,11,16,23,24].

Since the advent of angiography, the percentage of undiagnosed cases has been markedly reduced[1] However, colonoscopy has not become firmly established as a method for determining the site and cause of massive intestinal bleeding, but its importance as an intra-operative guide and its definitive value in intra-operative assessment of colonic disease has been discussed[20,25–27].

Rogers and Adler[27], Wolf *et al.*[6] and Steward *et al.*[9] have reported some patients in whom colonoscopy allowed diagnosis and treatment of lower massive intestinal bleeding. In 1985, Salem *et al.*[22] compared colonoscopy and selective visceral angiography in the diagnosis of colonic angiodysplasia. They pointed out that colonoscopy was helpful in demonstrating multiple sites of angiodysplasia and showed a good correlation between colonoscopy and selective visceral angiography in the diagnosis of colonic angiodysplasia. They also found 'that colonoscopy was of additional value in the diagnosis of concomitant disease, in establishing pre-operatively the site and extent of lesions before resection, and in affording the opportunity for electrocoagulation in suitable cases'[22].

Although angiography is generally considered to be the most important single procedure in the diagnosis of vascular ectasia of the colon[9] and, while elective operation has been recommended to remove the segment of colon which contains the bleeding lesion, we have employed colonoscopy for diagnosis and endoscopic fulguration as the treatment of choice for these small lesions. We did not find vascular lesions in 17 of our 34 patients with massive lower intestinal bleeding, but other lesions which were potential sources of haemorrhage were found (*Tables 1* and *2*). In our view, colonoscopy is the method of choice for the diagnosis of angiodysplasia and also allows the therapeutic possibility of fulguration.

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Fate of the ischaemic limb in Buerger's disease

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The clinical course of 328 patients with Buerger's disease (thrombo-angiitis obliterans: TAO) was followed. Neither ischaemic ulcers nor gangrene occurred in 26 per cent of the patients. Almost all of the ulcers occurred in patients between 20 and 50 years of age, with a peak incidence between 40 and 45 years. The younger the patient at the onset of the disease, the later the first ulcer occurred, and the later the first ulcer occurred, the shorter the period in which ulceration may recur. Recurrent ulcers were observed in 45 per cent of the patients. The progression of symptoms was influenced by smoking, but this was not the only deleterious factor as there were patients with stable TAO unaffected by smoking. In the 30 patients over the age of 60 years, ulceration and gangrene were not observed. In all patients, the progression of symptoms was self-limited and recurrent ulcers occurred less frequently with ageing. The rate of major amputation was low (3·9 per cent) although minor digital amputations were sometimes required. The survival rate of patients with TAO was higher than that of patients with arteriosclerosis obliterans. The aim of treatment in patients with TAO is to make patients abstain from smoking to prevent ulceration and to shorten the period of healing of trophic lesions without major amputation, as ulceration and gangrene in TAO are limited to the most distal part of the limbs, and seems to have healing potential.

Keywords: Thrombo-angiitis obliterans, ulceration, gangrene, tobacco smoking

Since the first report of a clinical disorder called endarteritis by Winiwater[1] in 1879 and later named thrombo-angiitis obliterans by Buerger[2] in 1908, the existence of thrombo-angiitis obliterans (TAO) as a disease entity separate from arteriosclerosis obliterans (ASO) had been challenged[3], although TAO is now recognized as a distinct clinical entity. Although many reports[4–12] have described the characteristic clinicopathological features, there are few reports[7,13,14] providing information about the natural course of TAO.

In this retrospective study, in which rigorous clinical criteria were used to differentiate patients with TAO from those with either ASO or other chronic arterial occlusive diseases, we examined those features of TAO which influence the prognosis.

Patients and methods

Patients

We evaluated the records of 328 patients with TAO, who had been treated or examined in the Department of Surgery at Nagoya University Branch Hospital from July 1968 to June 1985. They included 319 men and 9 women. Our clinical diagnostic criteria of TAO are: (1) a history of smoking; (2) age of onset of ischaemic symptoms <50 years; (3) infrapopliteal arterial occlusion; (4) upper limb involvement or phlebitis migrans, and (5) absence of risk factors of arteriosclerosis obliterans such as hypertension, hypercholesteraemia and diabetes mellitus. The clinical diagnosis of TAO was made when all five criteria were met. None of the patients had evidence of heart disease, collagen disease, popliteal entrapment syndrome or cystic adventitial disease of the popliteal artery. A total of 574 lower and 140 upper limbs were studied. Involvement of one or more infrapopliteal arteries was noted in all patients. The progression of the arterial occlusion to the suprapopliteal segment was recognized in 187 limbs (infra-inguinal segments, 148 limbs, supra-inguinal segments, 39 limbs). A total of 327 patients (99·7 per cent) had been smokers, 292 (89·0 per cent) had arterial occlusions in the upper limbs and 167 (50·9 per cent) had migrating thrombophlebitis. The mean age at the time of examination in our hospital was 41·2 years, ranging from 23 to 63 years. The mean age of the onset of disease was 35·6 years, ranging from 18 to 50 years (*Table 1*). The onset of the disease was noted in the second decade by 3 patients (0·9 per cent), by 83 (25·3 per cent) in the third decade, 135 (41·2 per cent) in the fourth decade and 107 (32·6 per cent) in the fifth decade. Of the 328 patients, 35 (10·7 per cent) had ischaemic symptoms only in the upper limbs, 224 (68·3 per cent) in the lower limbs and 69 (21·0 per cent) in both upper and lower limbs. Symptoms in the lower limbs at the time of the examination were as follows: 111 (19·3 per cent) were asymptomatic, 63 (11·0 per cent) had cyanosis and/or coldness, 106 (18·5 per cent) had claudication and 287 (50·0 per cent) had rest pain or ischaemic ulcers or gangrene. Forty upper limbs (28·6 per cent) had ulcerations. Ulcers and gangrene were most frequently located in the toe or finger, and no ulcer was observed beyond the ankle or wrist joint. Of the 328 patients, 289 (88·1 per cent) were followed up. The mean follow-up period was 4·8 years, ranging from 3 months to 18 years. The course of events in 489 lower (85·2 per cent) and 120 upper (85·7 per cent) limbs could be followed.

In 515 patients (453 men and 62 women) with ASO in the same period, comparisons were made regarding prognosis, including life expectancy. The mean age at the time of examination in our hospital was 65·5 years, ranging from 41 to 89 years. The mean age of onset of the disease was 63·5 years, ranging from 39 to 87 years. Four hundred and forty-four patients (86·2 per cent) were followed up for a mean period of 4·9 years, ranging from 3 months to 17·4 years (*Table 2*).

Table 1 *Clinical data on patients with Buerger's disease and arteriosclerosis obliterans*

Clinical data	Thrombo-angiitis obliterans	Arteriosclerosis obliterans
Total no. of patients	328	515
Male (%)	319 (97·3)	453 (88·0)
Female (%)	9 (2·7)	62 (12·0)
Mean age in years at examination (range)	41·2 (23–63)	65·5 (41–89)
Mean age in years at onset of disease (range)	35·6 (18–50)	63·5 (39–87)
Affected limbs		
Lower	574	697
Upper	140	0

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Table 2 *Follow-up results on patients with Buerger's disease and arteriosclerosis obliterans*

	Number of patients	
	Thrombo-angiitis obliterans	Arteriosclerosis obliterans
Patients	289	444
Deaths	8 (2·8%)	168 (37·8%)
Age at death, years (range)	47·9 (35–56)	72·1 (51–91)
Lower limbs	509	541
Major amputation	20 (3·9%)	48 (8·9%)
Upper limbs	120	0
Major amputation	2 (1·7%)	0

Treatment

Fourteen lower limbs in 12 patients had undergone previous arterial reconstruction because of claudication in five limbs and ischaemic ulcers or gangrene in nine. All of the grafts were occluded at the time of our first examination. A total of 74 lower limbs in 69 patients underwent arterial reconstruction (of the aorto-iliac segment in 24 limbs, and of the femoropopliteocrural segment in 50 limbs). Ischaemic symptoms for which reconstructive surgery was indicated were claudication in 28, rest pain in 5, and ulceration or gangrene in 41. Bypass grafting was performed on 70 limbs; 22 of these grafts were patent. Early graft failure (within 1 month) was recognized in 22, late graft failure in 21, and 5 were lost to follow-up. Thrombo-endarterectomy was performed in four extremities. On follow-up, three vessels were patent, and one was occluded. Two bypass operations were done on upper extremities, both in patients with symptoms of effort pain.

Lumbar sympathectomy (LSE) was performed for 352 limbs of 282 patients. Before the patients had visited our hospital, 99 (30·2 per cent) had undergone this procedure in 134 limbs (23·3 per cent); 35 procedures were bilateral. LSE was performed on 218 limbs (38·0 per cent) of 183 patients (55·8 per cent) in our hospital; 35 of these procedures were bilateral. Ischaemic symptoms for which LSE was indicated were cyanosis and/or coldness and/or claudication in 140, rest pain in 10 and ulceration or gangrene in 202.

Thoracic sympathectomy (TSE) was performed in a total of 66 limbs of 58 patients. Sixteen limbs of 12 patients, 4 of whom had bilateral procedures, underwent TSE in other hospitals. TSE was indicated for nine limbs with cyanosis and/or coldness, in one because of rest pain and in fifty-six limbs because of ischaemic ulcers.

Medical therapy was used for the patients with rest pain or ulceration, for whom neither arterial reconstruction nor sympathectomy was feasible. It was sometimes used as an adjuvant therapy for those with surgical treatment in order to shorten the period of ulcer healing. A continuous intra-arterial infusion with prostaglandin E1 (PGE_1), or an intermittent intravenous infusion with PGE_1 or PGI_2 was usually performed. Some patients had undergone such classical surgical procedures as a periarterial sympathectomy of the femoral artery, adrenomedullectomy, or extirpation of the carotid body.

Results

An analysis of the history of ischaemic ulcers and gangrene was performed covering the period 0·5–44 years from onset of the disease (the average being 12 years). Of the total of 328 patients, 289 were analysed on the basis of complete follow-up data obtained by a recent survey and the remaining 39 on the basis of data obtained at the last follow-up. In 85 patients (25·9 per cent) neither ulcers nor gangrene occurred; one or both occurred in 243 patients (74·1 per cent). In 157 patients (47·9 per cent), ulcers occurred only in the lower limbs; in 56 (17·1 per cent), they occurred in both upper and lower limbs, and in 30 (9·2 per cent), the ulcers were only in the upper limbs. With regard to the number of extremities involved, in 144 (43·9 per cent) only 1 limb was involved; in 63 (19·2 per cent) 2 limbs; in 20 (6·1 per cent) 3 limbs and in 16 (4·9 per cent), 4 limbs. With regard to the number of times ulceration occurred, 95 patients experienced ulceration on only one occasion and 148 patients (45·1 per cent) had ulcers on more than two occasions. The mean age of onset of TAO was 37·4 ± 7·1 years in cases without ulcers, 36·0 ± 7·1 years in those with only one episode of ulceration and 33·8 ± 7·8 years in those with repeated ulceration.

The age of onset of TAO in all patients, and age of onset of the first ulcer and last ulcer in 243 patients with ulceration are shown in *Figure 1*. The number of patients with ulcers are shown in 5-year age periods. The mean age of onset of TAO was 34·8 years, that of the first ulcer was 38·0 years, and that of the last ulcer was 42·0 years. We had 30 patients over the age of 60 years, who had had ischaemic ulcers earlier in their clinical course but no ulceration was noted after the age of 60 in these patients. We divided the patients with ischaemic ulcers into three groups: Group A included patients with onset of ulcers in the third decade; Group B with onset in the fourth decade; Group C with onset in the fifth decade. The mean age of onset of TAO was 25·1 years in Group A, 35·0 years in Group B and 43·8 years in Group C. When we calculated the period from the onset of symptoms to that of the first ulcer, we found significant differences among the three groups: the mean period was 6·8 ± 1·0 years in Group A, 3·1 ± 0·4 years in Group B, and 1·9 ± 0·3 years in Group C. In other words, the younger the age of onset of disease, the later the first ulcer occurred.

The duration from the age of onset of the first ulcer to that of the last one was also analysed: the mean period was 7·7 ± 0·8 years in Group A, 7·6 ± 0·7 years in Group B, and 5·1 ± 0·3 years in Group C. There were significant differences between Group A and Group C ($P<0\cdot05$), and between Group B and Group C ($P<0\cdot05$). This finding suggests that the later the first ulcer occurs, the shorter the period of possible recurrence.

Ischaemic ulcers developed after LSE in 96 of 331 lower limbs (excluding 21 limbs without follow-up), and in 15 of 58 limbs after TSE (excluding 8 limbs without follow-up). In the lower limbs with LSE, ulcers developed in 26 of 130 lower limbs with symptoms of cyanosis and/or coldness and/or claudication (excluding 10 limbs without follow-up) (20·0 per cent), and in 70 of 201 limbs with rest pain or ulcer (excluding 11 limbs without follow-up) (34·8 per cent, χ^2 test: $P=0\cdot002$). In the upper limbs with TSE, ulcers recurred in one of nine with a symptom of cyanosis and/or coldness and/or effort pain (12·5 per cent) and in fourteen of forty-eight limbs (excluding eight limbs without follow-up) with rest pain or ulcers (29·2 per cent, χ^2 test: $P=0\cdot5573$).

Of 289 patients, 127 (43·9 per cent) did not abstain from smoking despite intensive advice regarding its harmful effects. Of these, 61 (48·0 per cent) had ischaemic ulcers, but in about one-half of these patients no ulcer occurred despite continued tobacco usage. On the other hand, 16 (9·9 per cent) of the patients had ulcers even though they had stopped smoking. The rate of ulcer occurrence was significantly higher in the smoking group than in the non-smoking group (χ^2 test: $P<0\cdot0001$).

'Major amputation' is defined as an extremity without the distal (ankle or wrist) joint. Fourteen lower limbs of fourteen patients had previously undergone major amputations (ten amputations below the knee, and four above the knee). Ten

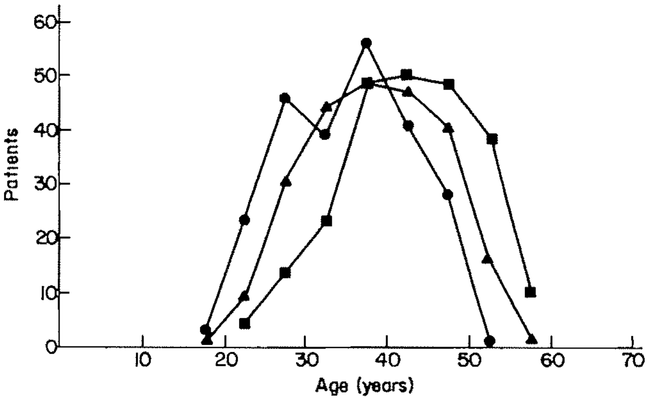

Figure 1 *Age at onset of TAO (●), age at onset of the first ulcer (▲) and age at onset of the last ulcer (■)*

below the knee and four above the knee amputations in twelve patients took place in our hospital; four below the knee, two above the knee and two forearm amputations took place in other hospitals after our first examination. The overall amputation rate for the lower extremity was 3·1 per cent, and for the upper, 1·7 per cent. The indications for major amputation in our hospital were as follows: 11 amputations took place after long hospitalization without evidence of ulcer healing despite surgical or medical therapy (continuous intra-arterial infusion of PGE_1 was not effective in six limbs); two amputations were undertaken because of acute progression of ischaemia after graft failure, and one was done after an accidental femoral fracture. Eleven of fourteen amputations were done in the limbs with suprapopliteal arterial occlusions.

Of 289 patients with TAO, only 8 (2·8 per cent) died during the follow-up period. Of the eight deaths, three were cardiogenic, three malignant, one was due to mesenteric arterial thrombosis and the other one was due to mesenteric venous thrombosis. The last two deaths were in the patients with juxtarenal aortic occlusions. In the patient with mesenteric venous thrombosis, an autopsy was performed: no pathological findings of TAO were observed in the visceral vessels. Of 444 patients with ASO, 168 (37·8 per cent) died during the same period.

Discussion

Of the various symptoms of TAO, coldness and claudication do not interfere markedly with the patient's daily life, but ulceration or gangrene are intolerable. A majority of the patients did not visit us until they had severe pain from an ischaemic ulcer. For this reason, in dealing with patients with TAO, it is important to know whether ischaemic ulcers will occur, when they tend to occur, and what the prognosis is for limbs with ulcers.

This study shows that no ulcers occurred in about one-quarter of the patients not lost to follow-up, about one-quarter had only one episode of ulceration, and the others had repeated episodes of ulceration. The clinical course of TAO can be divided into three types according to the pattern of occurrence of ulceration or gangrene: the ulcer-free type, the single-ulcer type and the recurrent ulcer type.

Almost all of the ulcers occurred in patients between the ages of 20 and 50 years, with the peak incidence between 40 and 45. It is noteworthy that the later the age of onset of ischaemic symptoms, the shorter the duration of suffering from ulcers or gangrene. The possibility of ulceration in patients over 50 years was extremely low, and no ulcers occurred in patients over the age of 60 years. Progression of ulceration with ageing was not found in this study. This is interesting when compared with the natural history of ASO, in which progressive deterioration is usually observed in the cases with ulceration or gangrene. The healing potential of ischaemic ulcers was proved in the majority of cases with TAO in our study using the non-invasive radioisotope thallium-201[15]. The extremely low rate of major amputation (2·5 per cent) in our series attests this fact. The prognosis of the extremities of patients with TAO is, thus, fundamentally good, although minor digital amputations are sometimes required. Wessler *et al.*[3] regarded TAO as an early demonstration of atherosclerosis in young individuals rather than as a distinct clinical entity, but the results of this study show that the clinical course of TAO does not result from degenerative changes of the arteries as does ASO. High major amputation rates for TAO have been reported in other institutions[7,16,17], However, it must be stressed that the aim of the treatment of the ulcers of TAO is to shorten the period of ulcer healing without major amputation. Although bypass operations are most effective for healing the ulceration, direct arterial surgery is rarely indicated in the patient with TAO because of poor run-off[18]. The results of LSE in patients with TAO have been reported by several investigators[14,19,20]; however, there are few critical reports on the long-term effects. LSE is sometimes effective for healing an ulcer or for preventing the occurrence of ulcers, especially in patients with mild ischaemic symptoms. If LSE fails to heal trophic lesions, a continuous intra-arterial or an intermittent intravenous infusion of PGE_1 is recommended.

The aetiological role of tobacco in this disorder is not clear, but the deleterious effects of tobacco usage have been stressed in every report. In this study, the rate of ulcer occurrence was higher in the patients who continued smoking than in those who abstained from it. However, it is of special interest that no progression of symptoms was observed in about one-half of the patients who continued smoking, and a few patients suffered from ischaemic ulcers even though they had abstained from tobacco. It is considered that the use of tobacco exerts a deleterious effect on patients with TAO, but there may be patients with a stable type of TAO, who are unaffected or less affected by smoking.

In our series, one patient with infrarenal aortic occlusion died due to mesenteric arterial thrombosis, and deaths resulting from mesenteric vascular occlusion have been reported by others[7,8,16,19]. Progression of secondary thrombosis proximal to the renal arteries was suspected in our case. For patients with high aortic occlusion, anticoagulant therapy may be useful. Coexistent atherosclerotic changes shown in patients with TAO, which have contributed to the controversy concerning whether TAO is a distinct entity, have been well recognized[2,10,19–21]. Inada and Katsumura[11] suggested that patients with TAO frequently also develop atherosclerosis obliterans, and at an earlier stage than normal people. Although three of our patients died from myocardial infarction, it is difficult to accept Inada and Katsumura's hypothesis because of our results regarding the good prognosis of the limbs and the low mortality rate in patients with TAO. McPherson[7] also suggested that the life expectancy of the patients with TAO is comparable to that of the general population. Further investigations must be carried out to confirm the relationship between the clinical course and the atherosclerotic process in patients with TAO.

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Case report

Br. J. Surg. 1988, Vol. 75, March, 262

Small bowel obstruction due to peritoneal encapsulation

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Peritoneal encapsulation is a rare condition in which the small bowel is contained within an accessory peritoneal sac. This sac is bounded by the omentum and mesocolon. The small bowel emerges by way of a small aperture. Peritoneal encapsulation is not associated with malrotation. The anatomy has previously been described in detail[1].

Peritoneal encapsulation is believed to arise during embryonic development when the small bowel lies temporarily within the physiological umbilical hernia. It is suggested that the duodenum then becomes adherent to the neck of the yolk sac and as the bowel returns to the abdomen the lining of the yolk sac is drawn with it[2].

Eight cases of peritoneal encapsulation have been reported in the literature and although some of these have been associated with intermittent abdominal pain, no case presenting as acute intestinal obstruction has previously been described[1–6].

Case report

A 56-year-old man presented with colicky abdominal pain. On examination he was found to have a tender abdominal swelling to the left of the umbilicus. Abdominal X-rays demonstrated a fluid-filled loop of small bowel which was situated in the left abdomen and which remained constant in position. Abdominal ultrasound examination also demonstrated a fluid-filled loop of bowel within the left abdomen.

Laparotomy was performed on the day of admission. The small bowel was found to be obstructed and contained within an accessory peritoneal sac which lay in the left abdomen, anterior to the colic vessels. The small bowel emerged from the sac behind the thickened neck of the peritoneal sac (*Figure 1*). This thickening was the cause of the obstruction. The obstructed bowel was viable.

The sac was opened, dividing the thickened neck, and excised. Postoperatively the patient made a complete recovery with relief of his symptoms.

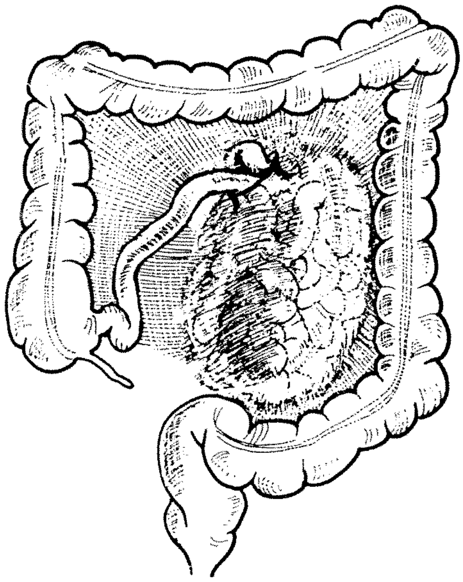

Figure 1 *The appearance of the peritoneal sac found at operation*

Discussion

It has been proposed that peritoneal encapsulation could safely be left alone when encountered as a chance finding as it rarely produced symptoms and has never been reported to produce intestinal obstruction[6]. However, in this case the condition has clearly been the cause of an acute small bowel obstruction requiring a laparotomy. As removal of the sac is simple and uncomplicated we suggest that this manoeuvre should be performed whenever the sac is encountered.

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263–266

Recurrent inguinal hernia: a personal study

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A personal series of 287 recurrent inguinal hernias repaired by a single consultant surgeon is presented. Four techniques of repair were employed in the series: Bassini operation; a posterior 'lace repair'; complete closure of the canal after division of the spermatic cord and local repair of isolated defects. The overall recurrence rate, 27 failures in 287 operations (9 per cent) is disappointing. The best technique is excision of the cord and canal closure, two failures in 43 operations (5 per cent). Cord excision does carry a risk of testicular complications.

Keyword: Recurrent inguinal hernia

In 1951 a project to determine the best technique of inguinal hernia repair was started in the United Liverpool Hospitals. The results of 2000 repairs were published in *The British Journal of Surgery* in 1958[1] and 1962[2]. The recurrence rate at 3 years after the operation for the repair of a recurrent inguinal hernia was 19 per cent. The present study is of 287 repairs in men where there had been a previous surgical intervention either by the author or by another surgeon.

Patients and methods

Diagnosis

The diagnosis of an inguinal hernia in a groin untouched by previous surgery is straightforward; this is not so when there has been a previous repair Two factors have changed—a localized bulge does not necessarily indicate a true recurrence, that is a deteriorating lesion, while a femoral hernia becomes much more difficult to distinguish from an inguinal.

Significance of a localized bulge In 19 cases a localized bulge noticed at reviews varying between 6 months and 8 years after operation did not increase in size at re-examination up to 20 years (mostly over 10 years) later. In five of them the bulge was not obvious at the latest examinations. Most bulges *did* deteriorate sufficiently to justify a further operation or the use of a truss. When this occurred, the change was obvious within 1 year, except in one case where nearly 2 years passed before a definite recurrence was recognized.

Differentiation from a femoral hernia A femoral hernia is more common after the repair of an inguinal hernia than in the previously unexplored groin, and particularly after the repair of a recurrent hernia. In this series of 287 men, 6 later developed a femoral hernia needing repair and 2 others have a marked femoral bulge. In two further cases femoral sacs were found during recurrent inguinal repairs.

In four cases, groin swellings diagnosed as recurrent inguinal hernias proved on exploration to be femoral hernias. In one of the six cases noted above, the rapidity of the appearance of the femoral sac (2 months after the recurrent inguinal repair) suggests that the preceding lesion was a *femoral* hernia misdiagnosed as inguinal as the operation notes record only 'moderate direct weakness'. It is often difficult to differentiate a recurrent inguinal hernia from a femoral hernia, perhaps because of the distortion of the position of the inguinal ligament by the previous intervention.

Pre-operative warning

Many recurrent hernias are best treated by a complete closure of the canal, especially if there has been more than one intervention. Sometimes this decision can be made only during the operation This should be discussed with the patient pre-operatively. If the closure of the canal is to be achieved by an excision of the spermatic cord alone, he will need to be warned of the probable and possible changes in the testicle after operation.

Morbidity

Injury to vas and vessels. In the 287 operations in this series the vas was accidentally divided on six occasions. Usually it was repaired, but no information is available as to the maintenance of its patency. The only later testicular change was the development of a spermatocele in one case 23 years later. In four other cases the testicular vessels were accidentally divided. In three men the testicle atrophied but more than 20 years later the fourth man appears to have a normal testicle, compared with the other side.

Excision of the spermatic cord stops short of the neck of the scrotum at or just below the external ring. Postoperatively the testicle becomes tender and swollen. The patient suffers moderate discomfort and has a low irregular pyrexia for some days. The swelling gradually diminishes in most cases to leave the man with a small hard testicle about one-third to one-half of normal size. In four cases, however, the testicle was apparently normal several years or more later. In one case the testicle sloughed, leading to a scrotal abscess from which the slough was removed 2 weeks after the hernia repair.

Infection. It is astonishing how much less frequent is postoperative infection in recent decades. In the first one-third of the cases (in the 1950s and 1960s), repaired mainly with silk, there were eight cases of deep-seated infection with subsequent sinus formation delaying healing for 5–18 months; two of these repairs later gave way. In the latter two-thirds of the cases (in the 1970s and 1980s), repaired mainly with a monofilament artificial fibre, there was only one case of deep-seated infection leading to a sinus which delayed healing for 5 months; this repair also gave way. This case occurred 15 years ago, since when there has not been a further case of deep infection.

Postoperative pain Patients complain more frequently of pain after a second inguinal repair than after a primary one, but the pain does not often last more than a few months. However, two patients were still complaining of intermittent discomfort in the inguinal scar 5 years after the operation.

Mortality

There were two deaths in the series.

1. In 1965 a man aged 61 years who had had two previous repairs presented with an irreducible mass in the left mid-inguinal region. Exploration revealed sliding iliac colon which was freed and pushed back, the 2 cm gap being closed with interrupted nylon sutures in two layers Within a few hours he displayed the classic picture of septic shock and died 48 h after the operation. Post-mortem examination revealed a lower abdominal purulent peritonitis without obvious injury to the intestine. Despite this it is probable that the large gut had been punctured at some stage of the repair, leading to the spreading infection.
2. The other death was of a man of 65 years who had had an excision of the spermatic cord to allow complete closure of the canal. This was the one case, referred to above, in which the testicle sloughed, yielding a scrotal abscess which was drained with removal of the slough 2 weeks after the repair. Eight days later, when apparently recovering satisfactorily, he died suddenly. Post-mortem examination revealed that he had had a coronary thrombosis.

Operation

The operation for the repair of a recurrent inguinal hernia is much more difficult than that of a primary hernia. Unless the previous type of repair is known, even the incision through the subcutaneous tissues must be done with extra care for the spermatic cord may have been transposed to this position: in this series the cord was found in this situation in 17

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Table 1 *Overall results of inguinal hernia repairs (recurrent cases in parentheses)*

	Method					
Type	Bassini	Lace	Closure of canal	Local repair	Others	Totals
Oblique	26 (3)	72 (4)	20 (0)	6 (0)	2 (1)	126 (8)
Oblique and direct	2 (0)	6 (0)	3 (0)	—	—	11 (0)
Direct	23 (1)	91 (10)	20 (2)	11 (4).	5 (2)	150 (19)
Totals	51 (4)	169 (14)	43 (2)	17 (4)	7 (3)	287 (27)

cases. In the inguinal canal the anatomy is often found to be very distorted, particularly if silk, thread or catgut has been used in the primary repair—less so if the suture material was an artificial fibre The leaves of the external oblique aponeurosis need to be dissected well back to expose the internal oblique and conjoint tendon above and the inguinal ligament below. The vas and vessels are at great risk during this dissection. The spermatic cord constituents may be scattered and the vas deferens in particular often lies much higher than one would expect, even 3 cm above the inguinal ligament The iliohypogastric and ilio-inguinal nerves are rarely seen. The consequent failure to prevent their entanglement in the posterior wall sutures probably accounts for the more frequent complaint of persistent postoperative pain after the repair of a recurrent hernia.

Multiple sacs are a much commoner finding in secondary repairs than in primary. In addition to the search during the clearance of the adhesions, finger exploration through the neck of an exposed sac, if possible, should identify from within any additional sac and the condition of the femoral canal

The recurrent hernias in this series were repaired by one of four methods:

1. Bassini-type operation in which the posterior wall of the inguinal canal is strengthened by apposing the conjoint tendon to the inguinal ligament,
2. A 'lace' operation, as described below;
3. A complete closure of the canal;
4. A local repair confined to the site of the recurrence.

Some cases would not fit under the above headings, for example repairs of a recurrence after a complete canal closure or when the conjoint tendon had been apposed to the pectineal ligament. They have been grouped under 'other methods'

Before excising an oblique sac and/or excising or invaginating with interrupted fine thread sutures a direct sac, the margins of the internal ring must be exposed. In many of the present cases under review the type of sac found at the previous operation was known and in 28 cases a direct hernia had been followed by an oblique recurrence, suggesting that in the process of strengthening the posterior wall the natural mechanism of the tightening of the internal ring during strains had been disturbed. At an operation for a direct recurrence the internal ring needs to be tightened, even when apparently normal The margins of the internal ring are more easily exposed if an oblique sac (or the spermatic cord if there is no oblique sac) is drawn laterally, allowing division of the cremasteric fascia at its attachment to the medial margins of the ring. This procedure exposes the dense fibres of the ring which, after the removal of an oblique sac (if present), can be apposed transversely with interrupted thread sutures to maintain the internal ring in its lateral position under the internal oblique. The cremasteric vessels will probably have been divided at the primary operation, but if they are found to be still present, passing across the medial part of the internal ring to interfere with its narrowing, they must be divided.

The posterior wall is now strengthened. In recent years a lace with an artificial monofilament fibre (polypropylene) has been used to achieve this. The suture is fixed in the region of the pubic spine, leaving the cut end at least 2 cm long to prevent slipping of the knot. It is then laced with multiple bites into the posterior wall from well up under the external oblique down to and through the inguinal ligament and back again, passing by short steps to the internal ring where the suture is passed through the previously sutured edge of the ring, under, upwards and laterally through the internal oblique for fixation well laterally in the aponeurosis of this muscle, when again the ends of the cut suture are left long. The correct tension of the continuous suture is found by pulling it tight after every five or six bites and then releasing it to find its own tension.

Finally, the external oblique is closed over the length of the canal. If, alternatively, it is decided to close the canal completely, the vas and vessels are divided separately at the internal ring and the spermatic cord excised to just beyond the external ring, not invading the neck of the scrotum unless there is associated testicular disease when an orchidectomy is carried out. The internal ring can then be closed completely with thread sutures and the polypropylene lace taken more laterally across the ring. The external oblique is closed tightly or overlapped over the posterior wall and closed internal ring

Results

It is very difficult to obtain comparable recurrence rates after varying methods of inguinal hernia repair, even within the same series[3]. Mudge and Hughes[4] have recently stressed the importance of 'the concept of late development of (recurrent) hernias'. The ages of the men reviewed ranged from 19 to 76 years, the average age being 53 years. In the present series there were 137 oblique sacs and 161 direct. Eleven patients had both oblique and direct sacs and one patient had two direct sacs (*Table 1*). In this series, in 69 cases (24 per cent) the previous repair had given way in the first year; in 110 cases (38 per cent) the previous repair had given way within 3 years; in 139 cases (48 per cent) the previous repair had given way within 5 years, and in 179 cases (62 per cent) the previous repair had given way within 10 years. Thereafter there was a steady trickle of further recurrences diminishing to one every other year in the fifth decade.

Cases have not been separated in accordance with the size and duration of each hernia but only according to its type, oblique or direct. As regards the physique, the age and the postoperative work of the patient, it may be that these factors are of less importance in obtaining comparable figures because of the balance between youth and better physique (improving the results) and the usual accompaniment of more severe postoperative strains (worsening them). These factors have not, therefore, been considered.

Of the 287 repairs, 27 have recurred, 17 were dealt with by further operation and 10 were given a truss. Two men with a non-deteriorating bulge also used trusses, one because he had a hernia on the other side and found a double truss more comfortable, the other because of his fear of the enlargement of the bulge although it had not increased over 14 years.

Forty-nine men have been lost to follow-up: thirty-eight died without review; the other eleven left the area and cannot be traced (at least three of these are probably dead). The remaining 238 men have been reviewed by the author, except in 11 cases where information was obtained by letter or telephone and in 5 cases reviewed by colleagues.

There were, therefore, eight recurrences following the repair of 137 recurrent inguinal hernias with oblique sacs (6 per cent) and nineteen recurrences following the repair of 161 with direct sacs (11 per cent). These 287 repairs were, however, not all of a recurrence of a previously repaired primary hernia. Many had been repaired two, three or even in one case four times previously, as follows: second operation, 258 cases, including 81 of the author's failures; third operation, 25 cases, including 11 of the author's failures; fourth operation, 3 cases, all the author's failures, and fifth operation, 1 case, the author's failure.

Second repairs

The results are shown in *Table 2*.

There were sufficient cases to allow the drawing of a life table

Table 2 *Total numbers of second inguinal hernia repairs (recurrent cases in parentheses)*

	Method					
Type	Bassini	Lace	Closure of canal	Local repair	Others	Totals
Oblique	23 (2)	71 (4)	18 (0)	5 (0)	2 (1)	119 (7)
Oblique and direct	2 (0)	5 (0)	1 (0)	—	—	8 (0)
Direct	22 (1)	86 (9)	11 (0)	10 (4)	2 (1)	131 (15)
Totals	47 (3)	162 (13)	30 (0)	15 (4)	4 (2)	258 (22)

Table 3 *Total numbers of third inguinal hernia repairs (recurrent cases in parentheses)*

	Method					
Type	Bassini	Lace	Closure of canal	Local repair	Others	Totals
Oblique	3 (1)	1 (Left the area)	2	1 (Died)	—	7 (1)
Oblique and direct	—	—	2	—	—	2
Direct	1	5 (1)	9 (2)	1	—	16 (3)
Totals	4 (1)	6 (1)	13 (2)	2	—	25 (4)

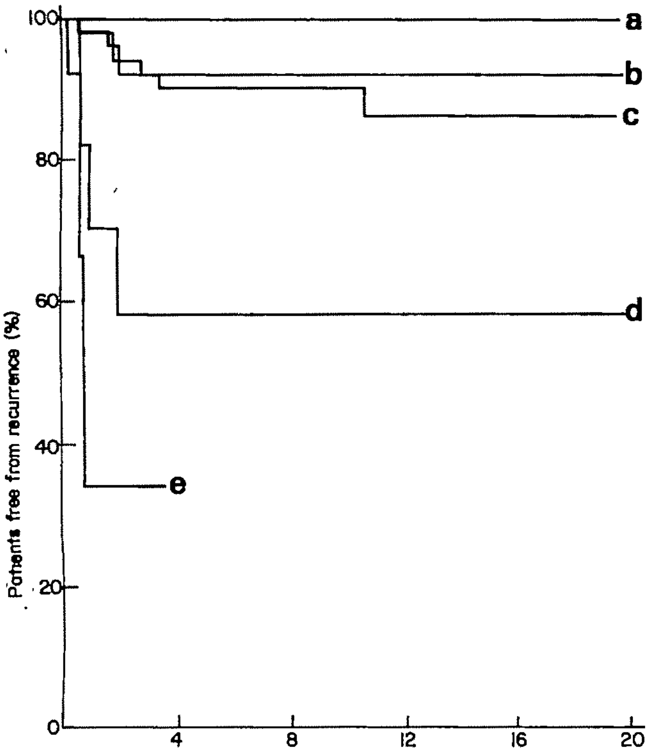

Figure 1 *Life table of results of second repairs (various methods).* **a**, *closure of canal;* **b**, *Bassini;* **c**, *lace,* **d**, *local repair;* **e**, *other methods*

(*Figure 1*). Overall, there were significant differences in recurrence rates between the five groups ($P<0\cdot0001$, logrank test[5]). Pairwise comparisons showed no significant differences between Bassini, lace and closure of canal. Similarly, there was no significant difference between local closure and other techniques. However, Bassini, lace and closure of canal were all significantly better than local closure and other methods.

Third repairs

Of the 25 cases, 23 were reviewed, 1 having left the area and another having died 48 h after the operation (as described previously). There were four recurrences, three of which were repaired and which are described under *Fourth repairs*. The fourth patient, who developed a deteriorating bulge 3 years after operation, was given a truss. The results are shown in *Table 3*. There were insufficient numbers to produce a life table but the length of follow-up of the different methods is given in *Table 4*.

Table 4 *Average length in years of follow-up of third repairs*

	Method			
Type	Bassini	Lace	Closure of canal	Local repair
Oblique	22	—	20	—
Oblique and direct	—	—	8	—
Direct	24	6	9	21

Fourth repairs

These were the three recurrences from the group of third repairs:

1. A previously direct recurrence repaired via a polypropylene lace at the third operation was found after 2 years to have both oblique and direct recurrent sacs. These were dealt with and a further lace inserted. The repair was satisfactory after 1 year.
2. A previously direct recurrence repaired via a complete closure of the inguinal canal at the third operation was found after 6 months to have a pubic recurrence. A polypropylene lace was used to repair the weakness and at review 6 years later the repair was sound.
3. A previously direct recurrence repaired via a complete closure of the inguinal canal at the third operation was found after 1 year to have a pubic recurrence. A polypropylene lace repair was carried out, but unfortunately the wound became infected and the hernia recurred in one year. Amazingly the man consented to a fifth repair.

Fifth repair

The recurrence was of the direct type. The sac was invaginated with a continuous silk suture and then monofilament polypropylene was laced into the posterior wall of the canal. Nine years later the repair appears to be satisfactory, although there is some bulging over the internal ring. Three years ago, however, a femoral hernia was repaired on this side.

Femoral hernia repair after repair of recurrent inguinal hernia

As well as the femoral hernia which developed after the solitary fifth inguinal repair just described, five other femoral hernias and two femoral bulges appeared after second operations. They were found at intervals varying from 2 months to 19 years after the inguinal repair, the average time being over 5 years. There was no special relationship to the type of repair but six (including the two bulges) followed the repair of direct inguinal recurrences in contrast to two after the repair of oblique ones.

Discussion

The results of my operations for recurrent inguinal hernia in men are disappointing. Twenty-seven failures in 287 operations is even at the best a minimum recurrence rate of 9 per cent. A more comparable figure, the rate of recurrence in the 238 that it was possible to review, is 11 per cent. This is far too high, even though the average follow-up is 10–15 years. When the results of the 287 operations are subdivided according to the method of repair (*Table 1*) the impressive results are those treated by the complete closure of the canal, for this method was used when there was pessimism about the likelihood of success.

When the results of second interventions only are considered (*Table 2*), the figures for complete canal closure are even more impressive in view of case selection. I was disappointed, however, that the lace method of repair had not proved to be superior to the Bassini-type repair, as I had expected; both were clearly superior to the local and other methods of repair. For third repairs the recurrence rate jumps to 16 per cent (*Tables 3* and *4*). The numbers are too small to compare methods of repairs but the two failures after complete closure of the canal are disturbing.

The results continue to deteriorate with one recurrence in the fourth repairs, but as yet the solitary fifth repair is sound after 9 years. Finally, there are the associated femoral hernias, apparently more common after the repair of direct recurrences, but otherwise without any relation to the different methods of inguinal repair.

Looking back over these results my own conclusions are as follows:

1. I regret that I did not use complete canal closure in more cases.
2. I am worried by the number of oblique recurrences in the second and third repairs. I suspect that in repairing some direct hernias, primary or secondary, I had not dealt adequately with the internal ring, which often appears to be normal. I may have concentrated my attention on the posterior wall repair, not fully appreciating that the tightening of this area may open up the internal ring.
3. With respect to the repair of the posterior wall, I had expected the lace technique to be superior to the Bassini. This was not supported by the results. Both are far from completely satisfactory and the use of a mesh would probably have improved my results. In the 1950s and 1960s the frequency of infection and consequent chronic sinuses after the use of nylon mesh, both in the United Liverpool Hospital series and in other published results, led to my having a marked prejudice against using a mesh. Now that infection is so rare I consider that I have been wrong in not using a mesh at least in some cases in recent years.
4. In the end the best solution to the problem of recurrent inguinal hernia is prevention: more care in, and improved techniques for, the repair of primary hernias.

Acknowledgements

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Diagnosis of Meleney's synergistic gangrene

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A retrospective and comparative study of 127 case reports of Meleney's postoperative progressive synergistic gangrene and of 62 examples of postoperative amoebic skin gangrene, showed that these two entities were clinically indistinguishable and that therefore a purely clinical diagnosis of Meleney's gangrene could not be made. Furthermore, a critical appraisal of the bacteriological data indicated that a certain diagnosis of Meleney's gangrene cannot be provided by the clinical bacteriologist. Finally, the histological features were entirely non-specific thus precluding a definitive diagnosis by the histopathologist. If Meleney's entity cannot be diagnosed its existence becomes debatable. The alternative diagnosis of cutaneous amoebiasis is advanced for consideration. Several of the outstanding features of Meleney's progressive gangrene, hitherto unexplained, are better understood if Entamoeba histolytica *is accepted as the prime cause rather than bacteria.*

Keywords: Meleney's synergistic gangrene, cutaneous amoebiasis

In 1924 Christopher from Chicago[1] and Cullen from Baltimore[2] independently reported single cases of progressive postoperative gangrene after empyema drainage and intraperitoneal abscess drainage, respectively. In 1926 Brewer and Meleney[3] from New York reported two similar examples of progressive gangrene that had followed appendicectomy, and when 21 cases were reviewed by Lynn[4] in 1931, all but one had occurred within the temperate northern zone of the USA. It is now clear that progressive postoperative gangrene emerged as an apparently new entity at the time when amoebic dysentery had become endemic throughout the northern half of the USA[5,6], but it is also clear that amoebiasis as a cause of the progressive gangrene was not considered in 20 of the 21 cases reviewed by Lynn[4], the exception being the case of postappendicectomy amoebic cutaneous gangrene reported by Cole and Heideman[7] in 1929.

Brewer and Meleney[3], after animal experiments with strains of a micro-aerophilic non-haemolytic streptococcus and of *Staphylococcus aureus* isolated from one of their cases, proposed that postoperative gangrene had a synergistic bacterial cause. Within a few years their results had become accepted world wide[8,9] and the entity eventually became known as Meleney's synergistic gangrene (MSG)[10].

However, a few authors had commented on the marked clinical similarities between MSG and cutaneous amoebiasis (CA)[11,12] and in 1967 Joseph and Bhat[13], reporting four cases of postoperative CA involving the abdominal wall, claimed that such cases had frequently been misdiagnosed as instances of MSG. We recently reported a further example of that error[14]; a diagnosis of MSG having been made on clinical grounds before the trophozoites of *Entamoeba histolytica* were recognized in biopsied tissue from the ulcer margin. Because the actual appearance of the amoebic gangrenous ulcer in our patient seemed to be identical to that depicted in a typical example of MSG[15] we undertook a review of 127 cases of MSG and 122 cases of CA (of which 62 were postoperative cases) and made a critical appraisal of the clinical, bacteriological and histological data from which a diagnosis of MSG has been achieved in the past.

Clinical diagnosis of MSG

Progressive postoperative gangrene became recognized as an entity with distinctive features that set it apart from more usual postoperative wound infections[16]. The topography was essentially truncal (*Figure 1a*), the onset was often delayed (10–14 days) and severe pain and inexorable progression were the outstanding clinical features. The ulcer presented a triple zone of colours[17]: an outer bright red zone, an inner raised purple margin and a central floor of red granulations partly obscured by grey or yellow exudate (*Figure 2*); the outline of the ulcer was sharply demarcated and serpiginous[12]. However, postoperative CA can exhibit precisely similar features. The topography is essentially truncal (*Figure 1b*) and the onset often delayed; severe pain and inexorable progression are characteristic[18]. The triple zonation of colour and the serpiginous outline exactly mimic those present in MSG (*Figures 2* and *3*)[19].

It must be accepted that, clinically, the two entities are indistinguishable and it follows that a certain diagnosis of MSG is not feasible on clinical grounds.

Bacteriological diagnosis of MSG

The frequent assumption[20,21] that a clinical diagnosis of MSG could be confirmed by the isolation of the micro-aerophilic non-haemolytic streptococcus with *S. aureus* from the lesions is unsound. The synergistic bacterial aetiology of MSG has not been correctly established. Firstly, in order to have proved a causal relationship between MSG and these two bacteria, it would have been necessary to show that they could not be isolated from infected postoperative wounds that had not become complicated by progressive gangrene. This essential control study has never been reported. On the contrary, the micro-aerophilic streptococcus has, as Meleney later reported[15], been isolated frequently from peritoneal exudates; this organism is probably identifiable as *Streptococcus milleri*[22] a commensal in the appendix lumen and frequently isolated from inflamed appendices[23]. Since *S. aureus* is a common pathogen of skin ulceration[24] it becomes difficult to see how two

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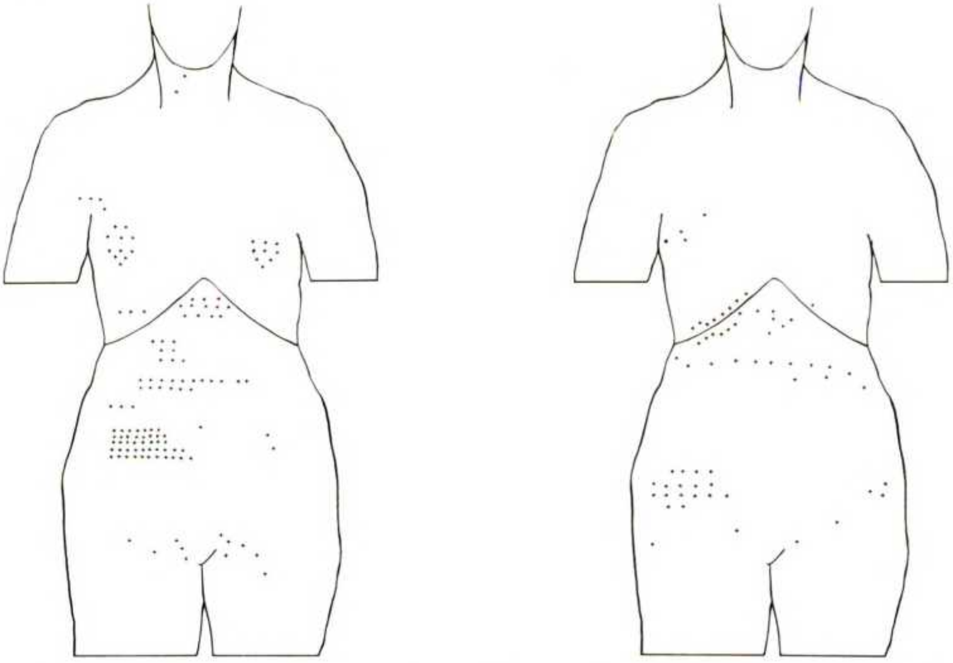

Figure 1 *Topography of* **a** *127 cases of Meleney's synergistic gangrene and* **b** *62 cases of postoperative cutaneous amoebiasis. The relative frequencies of the operation sites are shown diagrammatically.* **a** *There are 44 appendicectomies, 20 rib resections for empyema, and the remainder (63 cases) are scattered mostly over the anterior abdominal wall with only 2 cases following liver abscess surgery.* **b** *It should be noted that only 2 cases followed empyema surgery, there was a high incidence of liver abscess cases and relatively minor involvement of the right iliac fossa (5 appendicectomies, 3 paracaecal abscesses, 2 caecostomies) compared with* **a**

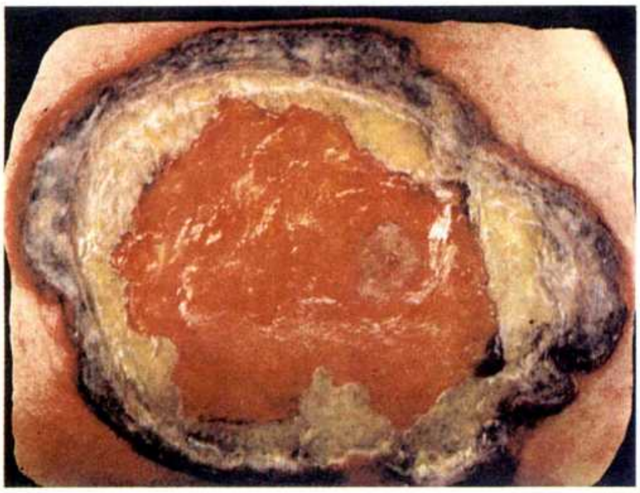

Figure 2 *Typical progressive bacterial synergistic gangrene of the chest wall after the drainage of an empyema**

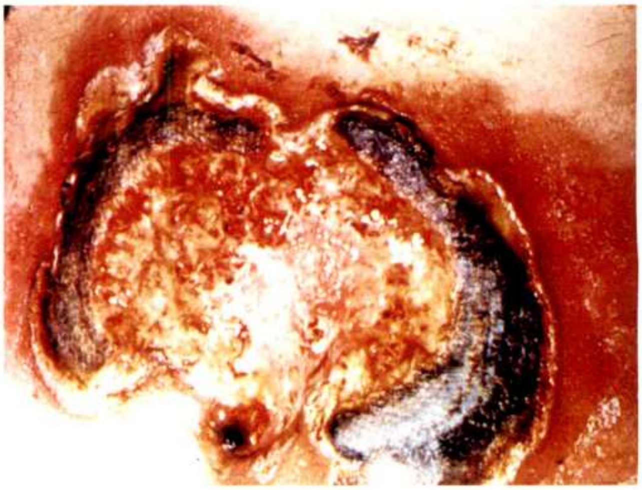

Figure 3 *Typical postoperative cutaneous amoebiasis of the abdomen after drainage of an amoebic abscess†*

such relatively common organisms could play a primary role in the aetiology of so rare an entity as MSG. Secondly, although synergism between bacteria isolated from the lesions of MSG was confirmed experimentally by several workers[25,26], progression of the gangrene was never produced; since progression is the outstanding feature of MSG, the consistent failure to reproduce it in the experimental animal detracts seriously from the value of the experimental evidence advanced to support the claim that MSG is essentially due to bacterial synergism. Thirdly, it has been shown that *Proteus* species could replace *S. aureus* in experimental synergism with the micro-aerophilic streptococcus[27] and, furthermore, synergism has been demonstrated experimentally between several different pairs of bacteria that may be found within the alimentary tract such as enterococci and *Escherichia coli*[28]. Thus synergism *per se* can now be seen as too widespread a potential event, particularly in the field of postoperative abdominal wound sepsis, for it to be invoked to explain the aetiology of so rare an entity as MSG.

It must be concluded that Meleney's laboratory studies failed to comply with Koch's postulates, and thus the diagnosis of MSG cannot be confirmed by the clinical microbiologist.

Histological diagnosis of MSG

The review of 127 cases of MSG provided no evidence that the histopathology was in any way specific; descriptions were often brief and in some cases absent. Autopsy reports were rare, largely owing to the success of surgery, and the histology of the gangrenous ulcer was not described[29,30]. Hirshfeld[31] described necrotic tissue densely infiltrated with neutrophil leucocytes and a deeper zone of granulation tissue. Poerschke[32] reported a mixed inflammatory cell infiltration at the edges of the ulcer while Neary and Rankin[33] noted extensive fragmentation of collagen and a marked inflammatory cell infiltration. It is quite clear that the histology of MSG is that of acute and subacute non-specific inflammation and has provided no clue to the aetiology of progressive postoperative gangrene. Equally, the non-specific character of the inflammatory response prevents the clinical histopathologist from making a definitive diagnosis of MSG.

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* *Reproduced with permission from Meleney*[15]

† *Reproduced with permission from Turner, Jones and Davson*[14]

Discussion

Since a positive diagnosis of MSG cannot be made on purely clinical grounds, or by the microbiologist or the histopathologist, the possibility arises that MSG may have an aetiology other than the bacterial synergism proposed by Brewer and Meleney[3]. We have already shown that CA when postoperative can exhibit the clinical features characteristic of MSG, so a logical step would be to examine the claim that *E. histolytica* can be considered as an alternative prime cause of MSG. Acute appendicitis is the commonest condition to be followed by MSG (*Figure 1a*)[34]. Consequently it has been generally assumed that the causal agent of MSG was an inhabitant of the alimentary tract; if so, then *E. histolytica* qualifies fully as such an inhabitant. The difficulty that the surgeon may experience clinically in distinguishing amoebic appendicitis or typhlitis from bacterial appendicitis is fully documented[35-37], and patients with right-sided amoebic colitis may not have clinical dysentery in the sense of bloody diarrhoea[37,38]. Thus, when invasive amoebiasis has become endemic in a temperate zone, and a patient presents with an apparent typical acute appendicitis, an amoebic aetiology will not be suspected. Appendicectomy may be followed, if the patient actually has amoebic colitis, by postoperative cutaneous amoebiasis[7,13]. Thus *E. histolytica* may well have been the unsuspected cause of postoperative gangrene when this complication has followed appendix abscess drainage[3], laparotomy for intraperitoneal abscess[2], paracaecal abscess drainage[39], colostomy[40], or retroperitoneal abscess drainage[41]. The second commonest condition to be followed by MSG was empyema (*Figure 1a*) and the possibility exists that rib resection and drainage may be carried out on a patient with entirely unsuspected underlying amoebiasis. Since the presentation of a patient with an amoebic empyema secondary to an amoebic liver abscess may be wholly respiratory[38,42], and since amoebic pus is not always typically 'anchovy' in colour[43], the amoebic origin of the empyema would not be suspected. Furthermore, when progressive gangrene developed around the drainage site, the diagnosis of MSG would be made[9,29] erroneously.

Thus an amoebic aetiology for postoperative gangrene arising in the right iliac fossa in the abdomen, or in the thorax after rib-resection, is likely since it is in these two locations that unsuspected invasive amoebiasis may clinically mimic bacterial appendicitis and bacterial empyema. The fact that these two sites figure so prominently in the frequency diagram for MSG (*Figure 1a*) provides strong support for *E. histolytica* as the preferred candidate agent for the aetiology of MSG. Moreover, several features, distinctive to MSG, can be better understood if *E. histolytica* is accepted as the cause. The severity of the pain in MSG has never been explained but, since excruciating pain is characteristic of CA[19], its occurrence in MSG favours amoebiasis as the cause. Similarly, the inexorable progression of MSG is easier to explain if *E. histolytica* is the true cause, since the inability of the patient to mount an effective defence against invasive amoebiasis in general[44], and against cutaneous amoebiasis in particular[45], is well known. Again, the absence of cross-infection in MSG has been noted[32,39] but not discussed; this absence is quite consistent with an amoebic cause since the trophozoites die rapidly after leaving the body and cysts, which could spread the infection, are not formed in the human tissues[46]. Finally, the undoubted success of surgery in MSG, limited in most cases to excision of the advancing ulcer edges, is difficult to reconcile with a bacterial aetiology of MSG since re-infection of the freshly incised tissues at the periphery could scarcely have been prevented if the infected floor of the ulcer had been left *in situ*. On the other hand it is known that in CA the trophozoites are largely confined to the advancing edges[47,48] and thus surgical excision may well be curative. To sum up, the four most distinctive features of MSG—the severity of the pain, the inexorable progression, the absence of cross-infection, and the success of limited surgical excisions—are more consistent with an amoebic causation than with a bacterial cause. This conclusion, if accepted, demands an explanation of why the amoebic aetiology of MSG could have been overlooked for so long. Explanations will be presented under three headings: clinical, microbiological and histopathological.

Reasons for failure to diagnose the amoebic aetiology of MSG

Clinical. Of primary importance was the prevailing low 'index of suspicion' for amoebiasis within the temperate regions of the USA where from 1924 onwards cases of postoperative progressive gangrene began to be reported[1-4]. Not until after the 1933 Chicago outbreak of amoebic dysentery, with its high postoperative mortality[49], was it recognized more widely that amoebic colitis could present as acute appendicitis[50,51] or as a paracaecal abscess[52]. Thus a surgically drained amoebic appendix abscess could be complicated by amoebic progressive gangrene without the protozoal aetiology being suspected. Similarly, a clinically silent amoebic liver abscess may rupture through the diaphragm with a resultant amoebic empyema; the clinical presentation may be purely respiratory[38,42] and, should amoebic cutaneous gangrene supervene after rib-resection and drainage, an erroneous diagnosis of MSG is made since amoebiasis was never suspected[1,9,29].

Microbiological. The presence of *E. histolytica* in purulent exudate from the lesion of MSG would not be detected in the course of the routine laboratory investigations, since it will not grow on the usual media (aerobic or anaerobic) employed in routine bacteriological investigations, nor would it be recognized in a Gram-stained film[53]; for its identification in pus a 'wet mount' microscopy search is needed[54]. Review of 127 case reports of MSG showed that this investigation was performed in only two cases[55,56]. Thus, for all practical purposes it can safely be concluded that amoebiasis was not properly excluded in the great majority of cases of MSG. Moreover, when the micro-aerophilic non-haemolytic streptococcus and *S. aureus* were both isolated from the lesion the clinical diagnosis of MSG would appear to have been confirmed fully[20,21] and hence further investigations to exclude amoebiasis would have seemed unnecessary.

Histopathological. Amoebic trophozoites can easily be missed in a section routinely stained by haematoxylin and eosin[57,58] or mistaken for macrophages[59]. The periodic acid-Schiff method is effective (*Figures 4* and *5*) and was first used for the detection of *E. histolytica* in biopsy material in 1962[60], by which date the great majority of case reports of MSG had been published and there is no evidence that this diagnostic aid had been used in any case of MSG. Not only may the trophozoites be overlooked when present in a section, but since they are irregularly distributed in 'nests', they may not be present in the section examined[61], and sometimes the wrong portion of tissue has been sent to the laboratory[62].

The histology of CA is essentially that of acute and subacute non-specific inflammation (*Figure 4*) and unless the trophozoites are present (and recognized) there is nothing in the histological picture to arouse a suspicion of amoebiasis; accordingly a specific and detailed search for *E. histolytica* may not be undertaken on the initiative of the histopathologist.

Thus there are cogent reasons for the amoebic aetiology of MSG to have escaped detection throughout the several decades following the first appearance of the entity in 1924.

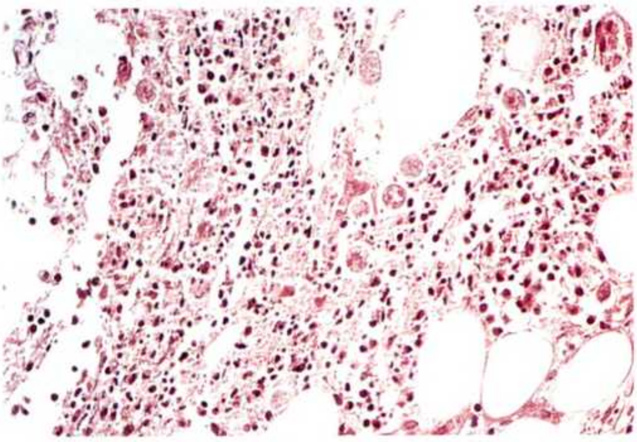

Figure 4 *Cutaneous amoebiasis. Biopsy from ulcer edge. The histology is that of non-specific inflammation in subcutaneous fat; the several trophozoites of* Entamoeba histolytica *that are present could be overlooked or mistaken for macrophages. Stained with haematoxylin and eosin,* × *170*

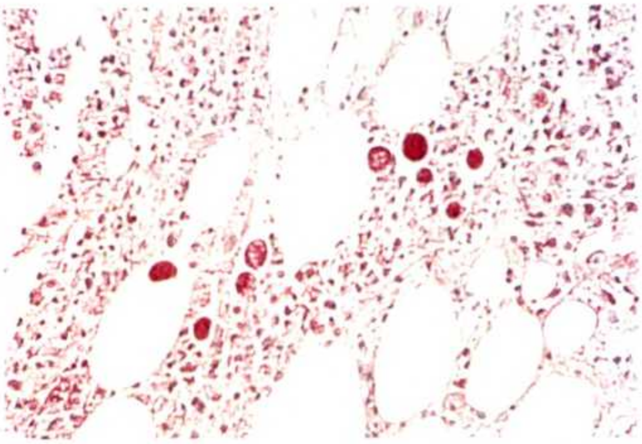

Figure 5 *Cutaneous amoebiasis. Adjacent section to* Figure 4. *The trophozoites stand out sharply when stained by the periodic acid-Schiff method,* × *170*

Significance of the location frequency differences between the lesions of MSG and CA

The right iliac fossa. Reference to *Figure 1* shows that the high frequency of appendicectomy cases followed by MSG is not seen to the same degree in CA which shows only a small number of postappendicectomy cases. Yet the caecum and appendix are frequently involved in amoebic colitis[18,36,37]; the paucity of numbers of postappendicectomy cases of CA seen in *Figure 1b* can most easily be explained if the expected cases have in fact occurred but have been misdiagnosed as MSG and are hence found in *Figure 1a*.

The thorax. The high frequency of MSG after empyema drainage is shown in *Figure 1a* and this contrasts strongly with the low incidence of CA after amoebic empyema drainage (*Figure 1b*). Yet amoebic empyema secondary to amoebic liver abscess is a well-known complication[18,38,42]; the unexpected paucity of instances of CA after empyema drainage is readily explained if the anticipated cases have been misdiagnosed as MSG and are therefore to be found in *Figure 1a*.

The right costal margin. It can be seen that only rarely did MSG follow liver abscess drainage (*Figure 1a*); once the presence of a liver abscess was known, the development of postoperative gangrene would be suspected to be of amoebic origin, and hence there would be a readiness to diagnose CA rather than MSG. In *Figure 1b* the close association between amoebic liver abscess and postoperative CA is demonstrated.

Thus, the distributional differences between MSG and CA as shown in *Figure 1* can be seen to have been determined almost entirely by the index of suspicion for amoebiasis. When the index is low, as in temperate climes, and patients have presented clinically as acute appendicitis or postpneumonic empyemata, then postoperative gangrene when it supervenes will be diagnosed as MSG. When the index of suspicion for amoebiasis is high, as in tropical climes or if a patient has a liver abscess, then postoperative gangrene will be diagnosed as CA. The survey of 127 cases of MSG shows that this entity has been almost entirely confined to countries of temperate climate; thus no cases have been reported from countries with a high prevalence of invasive amoebiasis such as India[63] or Mexico[64]. In such 'endemic areas' the preferred diagnosis, if postoperative progressive gangrene should develop, is CA[13,64] rather than MSG.

Due credit must still be given to Meleney for stressing the role of bacterial synergism in the field of postoperative wound infections, but it would seem that he misapplied the phenomenon of bacterial synergism to explain the aetiopathogenesis of postoperative progressive gangrene before another possible cause, *E. histolytica*, had first been fully excluded. It is not certain that recent case reports of MSG[22,65,66,67] correspond exactly with the distinctive clinical entity originally defined by Brewer and Meleney[3] in 1926; we do not suggest that such recent examples of synergistic bacterial gangrene are likely to have been due to underlying amoebiasis. Also, there is no doubt at all of the bacterial aetiology of necrotizing fasciitis[68,69]. Clinically, however, it remains important to distinguish accurately between postoperative CA which responds dramatically to emetine therapy[13,14] and postoperative necrotizing fasciitis which may require surgery[69].

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Gastric outlet loss and enterogastric reflux after gastrectomy

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The relationship of gastric secretion in response to a single injection of insulin and in response to a histamine infusion, before and after partial gastrectomy, was analysed in 58 patients. The aspirated gastric juice was corrected for gastric outlet loss and enterogastric reflux. Gastrectomy drastically reduced the stimulated gastric secretion by a similar proportion for the two secretagogues, thereby implying that antral gastrin plays no greater part in one than in the other. Gastric outlet losses were also reduced after gastrectomy, but as a fraction of gastric contents, both gastric outlet loss and enterogastric reflux more than doubled; the possible relationship of these findings to the aetiology of gastric ulcer is discussed.

Keywords: Partial gastrectomy, acid secretion, gastric outlet loss, enterogastric reflux

Partial gastrectomy has been used to produce a drastic reduction in the secretory capacity of the stomach. However, there is little available documentation of this reduction, perhaps because of the low incidence of recurrent ulceration after the operation—why quantify when there is no need to? Another reason may be the common assumption that there is difficulty in obtaining accurate measurements of aspirate from the stomach remnant.

We have developed methods for the measurement of the two main factors disturbing the quantification of gastric secretion, pyloric loss (called gastric outlet loss in this study), and duodenogastric (enterogastric) reflux. The former is measured by means of an extrinsic marker, phenol red, and the latter by an intrinsic marker, sodium ion.

Using these methods, we have sought to quantify the effect of gastrectomy on gastric secretion during insulin stimulation and histamine stimulation.

Patients and methods

Gastric secretion studies had been performed in 58 patients who had undergone a partial gastrectomy between 1966 and 1982. The gastric secretion tests were conducted as previously described[1].

A total of 40 of the subjects had a duodenal ulcer (31 men, 9 women, median age 46 years), of whom 38 were treated by Billroth II (13 after a previous vagotomy) and 2 by Billroth I partial gastrectomy. The remaining 18 subjects had a gastric ulcer (7 men, 11 women, median age 55 years), of whom 4 were treated by Billroth II, and 14 by Billroth I partial gastrectomy (1 after a previous vagotomy).

Gastric secretion was stimulated by two methods. First, the vagus was stimulated by an intravenous injection of insulin (0·2 units/kg); the subsequent gastric aspirate was collected for 120 min. The secretion during the last 90 min of this period was expressed as an hourly rate[1]. Secondly, maximal gastric secretion was elicited by a constant infusion of histamine (0·13 μmol/kg/h). This infusion was continued for at least 90 min and a plateau of secretion selected by computer to represent histamine-stimulated gastric secretion. An inert dye, phenol red, was infused at a constant rate throughout the test to permit the estimation of gastric outlet losses by the classic dye-dilution technique.

The sodium concentration of the aspirate was measured in order to be able to calculate enterogastric reflux[2]. It is well known that the sodium concentration of aspirated gastric juice falls as the rate of secretion increases. This phenomenon can be interpreted in terms of a two-component model: the mixing of an acid component of variable volume but fixed composition, and an alkaline component of small and constant volume and constant composition[3]. Accepting the findings of our study[4] that the alkaline component was mainly antral secretion with a volume of 10 ml/h and a sodium concentration the same as that of extracellular fluid, whereas pure gastric juice has a sodium concentration of 9 mmol/l, it is possible to estimate the expected sodium concentration for any given volume-rate of gastric juice. Any excess would then be of extragastric origin. If this is assumed to be from the duodenum, then the volume of duodenal fluid which has refluxed into the stomach can be calculated from the assumption that the sodium concentration of the refluxing fluid is 150 mmol/l. The method has been tested by the use of biliary markers[5,6], and the calculated volume of enterogastric reflux has correlated significantly with the measured quantity of marker found in the stomach.

In this study, of course, the alkaline component derived from the antrum would be reduced by the gastrectomy. However, trial calculations of enterogastric reflux, using an alkaline component of zero, gave increases in reflux volume of the order of only 10–20 per cent. As it is unlikely that all the alkaline component is from the antrum, the expected increases would be less than this, and so have been ignored.

Gastric secretion was measured as acid output (AO, mmol/h), gastric outlet loss-corrected gastric juice (V_{cor}, ml/h), and gastric outlet loss-(enterogastric reflux)-corrected gastric juice (V_g, ml/h) (reference 2).

Data are expressed as medians throughout, including the ratios of gastric secretion, as the data are severely skewed in some instances. Median ratios were found by calculating the individual ratios, ranking them, and finding the middle (median) ratio.

One test took place before we habitually used phenol red, and so a calculation of V_g could not be made: the number of tests available was, therefore, slightly smaller in some comparisons. For acid output, it was often the case that the aspirate was alkaline after the gastrectomy: ratios of secretion are, therefore, not given for acid output.

The Wilcoxon rank-sum test was used for all tests of statistical significance.

Results

Differences between the various sub-groups

For both insulin-stimulated and histamine-stimulated gastric secretion (acid output and V_g) after gastrectomy, there were no differences between those subjects who had had a previous vagotomy and those who had not. There were also no statistically significant differences between the corresponding values of gastric outlet loss and enterogastric reflux.

The same was true for gastric secretion and reflux within the comparisons of duodenal ulcer and gastric ulcer; Billroth I and Billroth II; and male and female patients.

However, for gastric outlet loss a consistent pattern was found: gastric ulcer patients lost less than duodenal ulcer

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Table 1 *Pre- and postgastrectomy gastric secretion*

	Insulin-stimulated		Histamine-stimulated	
n:	Pre-operative ($n=10$)	Postoperative ($n=31$)	Pre-operative ($n=9$)	Postoperative ($n=46$)
Acid output (mmol/h)	14·3	−0·1	32·7	1·5
V_g (ml/h)	174·0	23·4	248·4	56·4
Gastric outlet loss (ml/h)	49·5	17·4	30·0	16·5
As a percentage of V_g	28	74	12	45
Enterogastric reflux (ml/h)	39·6	22·8	0·6	30·6
As a percentage of V_g	23	58	<1	54

V_g, gastric outlet loss-(enterogastric reflux)-corrected gastric juice

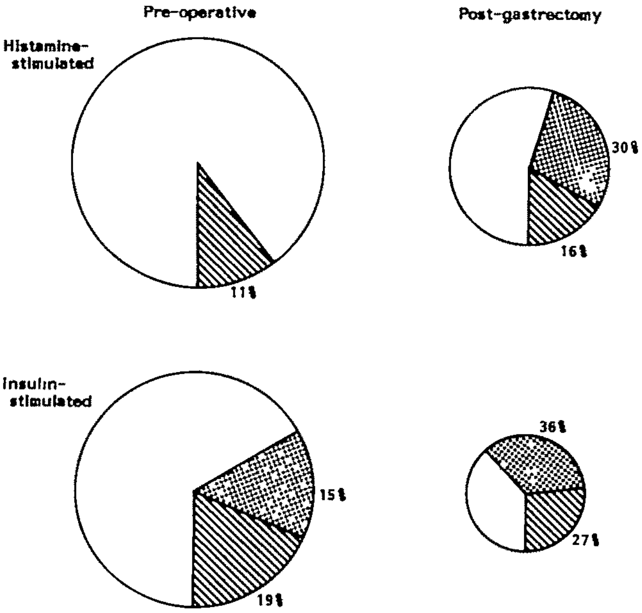

Figure 1 *Gastric outlet loss and enterogastric reflux before and after gastrectomy during insulin- or histamine-stimulated gastric secretion. The areas of the circles are proportional to the volume-rate of gastric juice.* □, V_g *(gastric outlet loss-(enterogastric reflux)-corrected gastric juice);* □, *reflux; and* ■, *loss*

patients, women lost less than men, and Billroth I patients lost less than Billroth II patients. The biggest difference was that between the DU and GU subjects during maximal histamine stimulation (35 ml/h *versus* 2 ml/h, $P=0·03$).

Effects of gastrectomy on insulin- and histamine-stimulated gastric secretion

As measured by the conventional criterion of (plateau) maximal acid output, gastrectomy was dramatically effective in reducing gastric secretion (*Table 1*). When insulin was the stimulus, 18 of the 31 patients had no titratable acidity in their gastric juice, and their aspirate was alkaline. The median acid output of all 31 patients was −0·1 mmol/h (i.e. titratable alkalinity was 0·1 mmol/h).

In terms of histamine-stimulated secretion, the reduction produced by gastrectomy was also large (95 per cent), but none of the patients showed complete histamine-fast achlorhydria.

After correction for gastric outlet losses and enterogastric reflux, it was apparent that patients after gastrectomy secreted rather more acid than the conventional estimates suggested. Nevertheless, the reductions of stimulated secretion were still large: 87 per cent for insulin-stimulated, 77 per cent for histamine-stimulated secretion. There was no significant difference between these reductions.

The median ratio of post-gastrectomy insulin- to histamine-stimulated secretion was 0·67 ($n=19$, range 0·09–3·33). This ratio did not differ significantly from the pre-operative ratio of 0·59 ($n=6$, range 0·39–0·85). The ratio in six tests was greater than 1·0.

Effects of gastrectomy on gastric outlet loss

There were losses via the pylorus in most patients before the operation, the median values being 49·5 ml/h for insulin-stimulated, 30 ml/h for histamine-stimulated secretion (*Table 1; Figure 1*). These medians were not significantly different. After gastrectomy, the absolute sizes of the losses were reduced to virtually the same median value irrespective of the stimulant, but their relative sizes in relation to gastric secretion sharply increased. This phenomenon was especially apparent with insulin-stimulated secretion, because of the smaller secretion evoked by this stimulus compared with histamine. Three-quarters of the gastric juice was lost; the corresponding fraction for histamine-stimulated secretion was also substantial, being close to one-half.

Effects of gastrectomy on enterogastric reflux

Before operation, there was no reflux during histamine-stimulation, but a significant reflux (23 per cent of V_g) with insulin (*Table 1, Figure 1*). After gastrectomy, reflux was significant with both stimulants and in absolute terms was about the same in magnitude as in the pre-operative patients during insulin stimulation. Irrespective of the stimulant, however, gastrectomy increased reflux as a proportion of gastric secretion to the region of 50 per cent.

Discussion

In this hospital, gastrectomy is no longer a common operation, except for carcinoma. Those peptic ulcer patients who did have a gastrectomy had particularly severe symptoms from their ulcer, or a recurrent ulcer following vagotomy, or else were treated several years ago when partial gastrectomy was more commonly used as a primary treatment for peptic ulcer. The numbers are therefore small, and may not be representative of the whole peptic ulcer population undergoing surgery.

Despite these reservations, it is clear that gastrectomy is very effective in reducing maximal gastric secretion, more so than vagotomy, as secretion was reduced to basal levels in most cases. Indeed, the post-gastrectomy measurements of acid output suggested that achlorhydria had been induced, but the alternative measurement of V_g showed that some secretion still persisted.

The insulin–histamine ratio did not differ significantly before and after the operation, and the proportional reductions for insulin-stimulated and histamine-stimulated secretion were also very similar. They were also not significantly different from the ratio (0·7) found in our larger pre-operative series[7], nor from an insulin–pentagastrin ratio (0·65) found in another post-gastrectomy sample[8]. These findings imply that, whatever the mechanisms of insulin and histamine stimulation, they are disrupted evenly throughout the gastric remnant. In addition, antral gastrin appears to play no greater part in vagal stimulation than in histamine stimulation of gastric secretion, as removal of the antrum seemed to have no greater effect on insulin-stimulated secretion than on histamine-stimulated secretion.

We found an 86 per cent reduction in gastric secretion (V_g) after gastrectomy, yet nothing like 86 per cent of the parietal cell mass was removed. This implies either that there is a greater concentration of parietal cells in the distal region of the body of the stomach, or that antral gastrin is a required potentiator for both insulin and histamine. However, the amount of reduction caused by gastrectomy appeared to be dependent on the measure of gastric secretion used, with acid output consistently giving greater reductions than V_g.

The acid output is dependent on the volume and titratable acidity of the aspirated gastric juice. The stoma after gastrectomy allows reflux of the alkaline duodenal contents, of variable volume, to influence this measurement. The percentage fall in acid is therefore likely to be greater than the actual reduction in gastric secretion unless collection errors are eliminated. The widely held belief that collection errors caused by the gastrectomy would make secretion studies unintelligible is not substantiated by our results. Our measurements show that gastric outlet loss and enterogastric reflux are in fact reduced by gastrectomy. However, because of the greater reduction in gastric secretion, they have proportionately increased. The elimination of such errors, of which the apparent achlorhydria after gastrectomy is an example, is therefore most important in the interpretation of the results.

The fact that gastric losses were higher in men than in women, and in patients with a duodenal ulcer, accords with the previous observation[9] that pyloric loss increases with the rate of gastric secretion. However, the higher gastric loss after Billroth II than after Billroth I could result from the type of operation, but is more likely to be due to the fact that most of the male patients had a duodenal ulcer and therefore had a Billroth II procedure.

Duodenogastric reflux has been suggested to be an important cause of gastric ulcer and occurs at greater than normal levels in gastric ulcer patients[10,11]. Patients with high gastric ulcer have low gastric secretion[12,13], and would therefore have a larger proportion of enterogastric reflux. The identical situation arises after gastrectomy and it might be expected, therefore, that gastric ulcer was a common complication of partial gastrectomy: this does not appear to be true. The difference is that, after gastrectomy, most if not all of the pyloric antrum has been removed. It has been reported[14] that, not only is the pyloric antrum of varying size and shape, but gastric ulcers occur only in the antral mucosa, or in the antral/fundic border[15,16], except for some associated with duodenal ulcer. It may be, therefore, the combination of enterogastric reflux and non-parietal mucosa that leads to gastric ulcer.

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Treatment policy for the management of carcinoma of the oesophagus

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The management of 120 consecutive patients with carcinoma of the oesophagus, treated in a district general hospital over a 10-year period is reviewed. The treatment options were by endoscopic methods, radiotherapy, surgery or a combination of these. Adenocarcinoma was the most frequent histological type (51 per cent) and 41 per cent of patients had squamous carcinoma. In addition to survival the quality of swallowing and the incidence of late complications following the treatment options was assessed. Primary surgery was carried out in 21 cases (operability rate 17·5 per cent) and 81 per cent of these cases were resectable. The overall operative mortality rate was 14·3 per cent (6 per cent in resected cases) and the 5-year survival rate was 9·5 per cent. After primary radiotherapy only 5 per cent of patients survived 2 years. The majority of patients were treated by endoscopic intubation with an overall mortality of 16·6 per cent and a mean survival of 5·5 months. Patients treated surgically experienced the best symptomatic relief and had the lowest incidence of late complications, when compared with those treated differently. However the overall results of surgery were poor and there remains the need to compare the results of surgery and radiotherapy in similar groups of patients.

Keywords: Oesophageal neoplasms, oesophageal stenosis, dysphagia, deglutition disorders, endoscopic dilatation, endoscopic intubation, radiotherapy, surgery

Carcinoma of the oesophagus continues to have a poor prognosis with 5-year survival rates for squamous cell carcinoma reported at 4 per cent by Earlam and Cunha Melo[1] and 5 per cent by Popp *et al.*[2]. In 1976 the treatment options available at North Tees General Hospital were defined: these include endoscopy alone, endoscopic dilatation, endoscopic intubation, surgical resection or radiotherapy, or occasionally a combination of these treatments. Important factors in determining the definitive treatment included the patient's age, cardiorespiratory status, the length of stricture, the presence or absence of metastases or associated malignancy and the histological type of the tumour. In 1986 the records of 120 consecutive patients with carcinoma of the oesophagus managed at the North Tees General Hospital over a 10-year period were reviewed. In assessing quality of life following treatment the two aspects considered were the quality of swallowing and the incidence of late complications requiring further management in hospital.

Patients and methods

One hundred and twenty consecutive patients presented to the GI Unit between 1976 and 1986 at North Tees General Hospital and their records were analysed. There were 75 men and 45 women, with an age range of 49–84 years. Dysphagia was the usual form of presentation and was categorized as follows: 0, nil; 1, avoidance of certain foods; 2, some solids avoided; 3, fluids only, 4, complete dysphagia[3] Most of the patients had Grade 3 or 4 dysphagia (63/120, 53 per cent) Those who ultimately underwent palliative intubation had particularly severe dysphagia (46/66, 70 per cent (Grade 4); 18/66, 27 per cent (Grade 3)). Investigations included routine haematological and biochemical parameters, liver function tests, chest radiographs, barium swallow (in the majority of patients), endoscopy (in all patients), and abdominal ultrasound but not routine computerized tomography. Respiratory function tests and an ECG were obtained in patients considered for surgical resection.

Tumours were divided into those sited in the upper, middle and lower third. For the purpose of defining the level of tumour the oesophagus between the jugular vein and the tracheal bifurcation was regarded as the upper oesophagus and that between the bifurcation and the oesophagogastric junction was divided equally into middle and lower thirds. Tumours were located in the upper oesophagus in 8 patients, in the middle oesophagus in 43 and in the lower oesophagus in 69 patients. Histological findings, which were obtained in all cases, revealed adenocarcinoma to be the most frequent type of tumour (61/120, 50·8 per cent) while 49 (40·8 per cent) of the lesions were squamous cell carcinoma and 5 undifferentiated. Five further patients had tumours of metastatic origin (breast, pancreas and bronchus). Patients under 65 years of age with strictures less than 8 cm in length as assessed endoscopically, with good cardiorespiratory function, with no overt metastases and with squamous carcinoma or adenocarcinoma were considered as potential surgical candidates. Those patients with squamous carcinoma who were not suitable candidates for surgery were treated by radiotherapy. Patients with adenocarcinoma unsuitable for surgery or with squamous cell carcinoma unsuitable for either surgery or radiotherapy by virtue of age or presence of metastases were managed by endoscopy (with or without dilatation) or endoscopy and intubation Endoscopy alone was used if the stricture was easily negotiated by the endoscope and would not readily support a tube, but in the remaining majority, Eder–Puestow dilatation was used and in most of these patients a modified Celestin or an Atkinson tube was inserted. All endoscopic procedures were performed under diazepam sedation. The characteristics of the patients in the different treatment groups are summarized in *Table 1*.

The mortality associated with all forms of management was assessed at 1 month.

Results

Treatment and immediate outcome

Endoscopy alone as a form of treatment was used in 12 patients. There were three perforations: one was managed successfully by surgery and two were treated conservatively; one of the latter subsequently died. One further patient died from carcinomatosis. Endoscopy with dilatation was used to treat four cases. One patient died from haemorrhage.

Endoscopy with intubation was used as a primary form of treatment in 57 cases; 5 of these received radiotherapy subsequently. A further six patients were treated by intubation after primary radiotherapy and another three after surgery. The total number of patients intubated endoscopically was therefore

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Table 1 *Patient details in the different treatment groups*

Primary treatment	Total no. of patients	Age >65 years	Stricture >8 cm	Poor cardiorespiratory function	Associated malignancy	Presence of metastases	Dementia	Histology: Squamous cell carcinoma	Adeno-carcinoma	Anaplastic carcinoma	Other
Endoscopy only	12	9	2	5	1	2	—	3	6	2	1
Dilatation	4	3	—	1	1	—	—	2	2	—	—
Intubation	57	38	11	20	—	22	1	14	40	—	3
Surgery	21	5	1	1	—	—	—	10	11	—	—
Radiotherapy	26	20	3	13	—	2	—	20	2	3	1

Table 2 *Survival time in the five treatment groups*

Survival time	Endoscopy ($n=12$)	Dilatation ($n=4$)	Intubation ($n=57$)	Surgery ($n=21$)	Radiotherapy ($n=33$)*
<1 month	2	1	11	3	—
<6 months	7	2	29	5	13
6–12 months	3	1	11	5	13
12–24 months	—	—	4	3	6
2–3 years	—	—	2	3	1
>3 years	—	—	—	2	—

* Includes 19 patients having radical radiotherapy and 14 patients having palliative radiotherapy; this latter group included 5 patients intubated endoscopically and 2 patients who had had surgical resection. No patient after palliative radiotherapy survived a year

66. The procedure was complicated by eight perforations, six of which were fatal. There were five additional deaths within 1 month, two from cardiovascular causes, two from carcinomatosis and one from aspiration pneumonia. Late complications are discussed below. The 1-month mortality in these cases was 11/57 (19 per cent) or 11/66 (17 per cent) if those patients who were intubated after radiotherapy and surgery are included.

Surgery was carried out in 21 of the 120 patients. In 17 cases the tumour proved resectable, the resectability rate being 80·9 per cent. Of the unresectable cases, two were intubated at the time of surgery and two were intubated endoscopically. One further patient was intubated endoscopically 3 months after surgery because of tumour recurrence. Two patients had radiotherapy following surgery. Of the 17 resectable tumours, 13 were situated at the lower end of the oesophagus and 4 in the middle third. Sixteen patients underwent the Ivor Lewis procedure and one a three-stage McKeown oesophagectomy[4]. Stapling techniques were used in 13 patients and 16 patients had a pyloromyotomy. Complications were mainly pulmonary, in the form of atelectasis, sepsis and pleural effusion (12 cases). Three patients died within a month of surgery, one from anastomotic leakage and two after surgical intubation of unresectable tumours. The operative mortality was therefore 14 per cent (3/21). In those patients who underwent successful resection the operative mortality was 6 per cent (1/17).

Radiotherapy was the primary form of treatment in 26 patients, although a further 5 received radiotherapy after intubation and 2 after surgery (33 in total). Nineteen patients received radical radiotherapy with dosages varying from 4750 to 5750 cGy. Fourteen patients therefore received palliative therapy. In those receiving radical therapy, complications included transient dysphagia in seven cases, late dysphagia due to fibrosis in four, and tumour recurrence in eight. Pneumonitis occurred in one patient. Dysphagia was managed by endoscopic dilatation or endoscopic intubation. No patient died within a month of initiating radiotherapy.

Survival (Table 2)

Of the patients treated by endoscopy alone or endoscopic dilatation, none survived a year. After endoscopic intubation the mean survival was 5·5 months and six patients (6/57, 11 per cent) survived a year. Two patients survived for 2 years. One of these received radiotherapy for a squamous carcinoma while the other was a demented 80-year-old lady with a well-differentiated squamous carcinoma treated by intubation alone.

After surgery, the survival rate at 1 year was 38 per cent (8/21), at 2 years 24 per cent (5/21), and 10 per cent (2/21) at 5 years. In the 17 patients undergoing successful resection the comparative figures were 47 per cent, 29 per cent and 11 per cent.

The survival rate after radical radiotherapy was 37 per cent (7/19) and 5 per cent (1/19) at 1 and 2 years respectively; no patient survived to 3 years; no patient who received palliative radiotherapy survived a year.

Late complications (Table 3)

There were no significant late complications requiring further management after endoscopy alone or endoscopy with dilatation, because of the short survival in these two groups. After endoscopic intubation there were 37 complications in 23 patients necessitating readmission: these included tube migration, tumour overgrowth, tube deterioration and bolus obstruction. In those who had undergone successful resectional surgery, one patient required endoscopic intubation and two needed radiotherapy for symptomatic relief after tumour recurrence. In the 26 patients who underwent primary radical or palliative radiotherapy, endoscopic management for symptomatic relief from dysphagia was required in 10 patients. Thus in the series as a whole, late complications necessitated readmission on 50 occasions in 36 patients, but the rate of readmission was twice as high in the endoscopic intubation and radiotherapy groups, compared with that in the group treated by surgery.

Quality of swallowing

The quality of swallowing was best after surgery. Thus 82 per cent of patients had normal swallowing and 18 per cent Grade 1–2 swallowing. After radiotherapy, however, only 15 per cent of patients had normal swallowing and 62 per cent Grade 1–2 swallowing, the rest experiencing greater difficulty in swallowing. After endoscopic intubation no patient had normal swallowing, 68 per cent of patients had Grade 1–2 difficulty with swallowing and 32 per cent had Grade 3–4 problems. This group of patients were those with the most severe dysphagia at presentation (97 per cent Grade 3–4).

Table 3 *Late complications in the three main treatment groups*

Mode of treatment	No. of patients	Number of late complications necessitating readmission	No. of patients with complications	No. of readmissions	Patients readmitted (%)
Endoscopic intubation	66	Tube migration (12)	8	37*	34·8*
		Tube overgrowth (10)	6		
		Tube deterioration (1)	1		
		Bolus obstruction (14)	8		
Resection surgery	17	Recurrence treated by endoscopic intubation	1	3	17·6
		Recurrence treated by radiotherapy	2		
Radiotherapy	26	Fibrosis treated by endoscopic dilatation	1	10	38·5
		Recurrence treated by endoscopic dilatation	6		
		Recurrence treated by endoscopic intubation	3		

* Data from 23 patients

Discussion

North Tees General Hospital is the only district general hospital serving a population of 200 000. There is a single endoscopic unit which investigates all patients with dysphagia. The incidence of malignant dysphagia in this district has previously been assessed during the years 1976–81 and was found to involve 7 individuals per 100 000 per year which is similar to the incidence figures quoted for elsewhere in the UK and Ireland[5]. The series presented here, therefore, reflects the total incidence of this problem over the 10-year period.

In this series, as in many others, there is a bias in that better patients were selected for surgical management. Thus, patients considered for surgical resection were mainly younger than 65 years of age[6,7], with good cardiorespiratory function[5,6], a stricture length less than 8 cm[8] and no distant metastases or associated malignancy.

The resectability rate in this group was 81 per cent. This compares well with rates reported in the literature (45–81 per cent)[5,9,10]. The operability rate, however, was low at 21/120 cases (17·5 per cent). Although the long-term results of surgery are disappointing, it may be argued that perhaps some patients have been deprived of the benefits of resectional surgery. However, any attempts to increase operability rates must not be made at the cost of a widening gap between operability and resectability rates, as this is likely to have an adverse effect on operative mortality. The role of bronchoscopy, ultrasonography, nuclear scintigraphy and CT scanning in the assessment of patients is undecided and these techniques were not used routinely in this series[11–15].

Chest infections and pleural effusion were the commonest complication, occurring in 12 patients, despite intensive pre-operative and postoperative chest physiotherapy. Only one anastomotic leak occurred (6 per cent of resected cases), which compares well with the 4 per cent rate reported by Huang *et al.*[10]. The use of a stapled anastomosis may have contributed to the low leakage rate, as has been suggested by Postlethwait[16]. The overall mortality in the surgically treated groups was 14 per cent and this figure includes the two patients treated by surgical intubation (both of whom died). High mortality rates for surgical intubation have been reported by others[17], and the procedure is no longer carried out in our Unit. Thus the mortality rate for the resectable group was 1/17 cases (6 per cent) which compares well with the 1·7–20 per cent rate reported in the literature[1,4,9,10,18].

The reported results of surgical management for carcinoma of the oesophagus are difficult to interpret because of the division of carcinoma patients into operable and resectable groups. If mortality and 5-year survival figures are expressed for all operated patients, then the results are discouraging, especially in the series which have low resectability rates. Overall mortality figures are of the order of 15 per cent (14 per cent in this series) and overall 5-year survival rates are unlikely to be over 10 per cent (9·5 per cent in this series). Clearly, the more selective policy employed here has not produced results which are better than those of other published series.

Most of the patients given radical radiotherapy in this series were over 65 years of age. Of 26 patients given radical primary treatment, 13 (50 per cent) also had poor cardiorespiratory function and 3 patients had long strictures (>8 cm) (*Table 1*). Thus a comparison of the results of treatment of patients with squamous cell carcinoma treated by surgery and radiotherapy is not valid. This is the drawback in most reported series in that radiotherapy is usually reserved for more advanced cases[19].

The results of radiotherapy were not encouraging. The 1-year and 2-year survival rates of 37 per cent and 5 per cent none the less compare favourably with mean figures of 18 per cent and 8 per cent in the literature[19]. Pearson's 5-year survival rate of 20 per cent[20] has never been reproduced, but recently Newaishy *et al.*[21] have reported crude 5-year survival rates of 9 per cent which compare favourably with the surgical survival figures.

In this series, the main early complication following radiotherapy was transient dysphagia, which occurred in seven cases. Late complications included tumour recurrence in eight cases and dysphagia due to radiation fibrosis in four cases, the frequency of the latter problem compares very favourably with the 43·7 per cent incidence of fibrous stricture reported by Newaishy *et al.*[21]. Both complications required in-patient dilatation or intubation in 10 of the 12 patients.

Primary endoscopic intubation was used in a total of 57 patients. These patients were very debilitated and most of them (58 per cent) were over the age of 65 years, with either a stricture longer than 8 cm, distant metastases or, more significantly, impaired cardiorespiratory function, all contra-indicating a surgical approach.

Endoscopic intubation is the commonest mode of palliation in such patients[3]. It gives considerable relief of dysphagia and may provide relative symptom-free survival for many months. Perforation of the oesophagus is the main complication. In the present series of 57 cases undergoing primary intubation, 6 patients undergoing intubation after radiotherapy and 3 being intubated after surgery, perforation occurred in 8 cases (8/66, 12 per cent), a rate similar to that reported in other series[3,22]. Although managed actively with intravenous fluids and broad-spectrum antibiotics, only two of the eight patients survived. The overall mortality of 19 per cent (or 17 per cent if all cases are included) is similar to that reported in the literature (11–23·6 per cent)[3,6,23]. Mean survival was short (5·5 months), although others have obtained marginally longer survival times (10·8 months)[6]. It is clear that after intubation the mortality and the incidence of late complications (*Table 3*) is appreciable and the quality of swallowing is poor. In addition, the patient's awareness that nothing has been done to curb the growth of the tumour contributes to low morale. In some patients we have succeeded in keeping tumours open by outpatient dilatation with Hurst mercury bougies. Our early practice of endoscopic intubation before radiotherapy was abandoned.

It is clear that surgery provides the best symptomatic relief, but the overall results are poor. The challenge is clearly to determine whether radiotherapy can do as well as, or better than, surgery; although our radiotherapy results are disappointing the patients chosen for elective radical radiotherapy were less fit and had more extensive lesions than those selected for operation. In this context there is a clear need for the trial recently initiated by the MRC to compare these two methods of management. Meanwhile, in spite of its hazards, endoscopic intubation does appear to offer significant palliation for the majority of patients, although laser therapy may be a valuable alternative in some patients[24].

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Relationship between gastric emptying of liquid and postvagotomy diarrhoea

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Gastric emptying of liquid was studied in 10 normal volunteers and in 27 patients previously treated with truncal vagotomy and drainage. Thirteen of the twenty-seven patients complained of persistent postvagotomy diarrhoea. For each study 300 ml 15 per cent dextrose, labelled with ^{99m}Tc-diethylene triamine penta-acetic acid (DTPA), was ingested at a standard rate by subjects who sat facing a gamma camera. Imaging proceeded for 30 min. Gastric area activity curves were corrected for emptying of the test meal during ingestion, and for movement using a new image alignment technique. Gastric emptying at 15 min was 10 ± 2·6 per cent (mean ± s.e.m.) in healthy volunteers, 48 ± 7·3 per cent in patients without diarrhoea, and 84 ± 2·3 per cent in those with diarrhoea (P < 0·001, ANOVA). Gastric emptying from 15 min onwards was slower than normal in both patient groups (P < 0·001). These results show that initial gastric emptying is rapid following truncal vagotomy and drainage, and this change is greater in patients with postvagotomy diarrhoea. No patient with diarrhoea had normal initial gastric emptying.

Keywords: Gastric emptying, postvagotomy diarrhoea, gamma camera imaging

The operation of truncal vagotomy with drainage (TV + D) is still frequently performed to treat complications of peptic ulceration. Many patients so treated develop troublesome diarrhoea, and for a few this complication is permanent and incapacitating[1]. Truncal vagotomy produces many physiological disturbances which, in theory, could cause diarrhoea. Clinically their relative importance remains uncertain, making the treatment of postvagotomy diarrhoea somewhat empirical.

Earlier workers reported that initial gastric emptying was greater in patients with diarrhoea than in those without diarrhoea[2]. Remedial surgical procedures aimed at delaying gastric emptying have thus been advocated for the treatment of postvagotomy diarrhoea. However, in a more recent study others have failed to demonstrate a difference in gastric emptying between patients with and without postvagotomy diarrhoea, and have questioned the emphasis on slowing emptying as a means of treatment[3]. In the present study we re-examined gastric emptying in patients with and without diarrhoea following TV + D, using more precise methods to quantify emptying in the early postprandial period.

Patients and methods

Gastric emptying was measured in 10 healthy volunteers, 14 patients without diarrhoea and 13 with diarrhoea following TV + D. Diarrhoea was defined as the passage of liquid stools three or more times daily[2]. Details of age, sex, and previous surgical procedures are summarized in *Table 1*. The healthy volunteers were younger than the patients, but there was no age difference between the two groups of patients. Thirteen of the fourteen patients without diarrhoea had previously undergone truncal vagotomy and pyloroplasty (TV + P), compared with only seven of the thirteen patients with diarrhoea. The pattern of diarrhoea was continuous in six subjects and intermittent in the remainder.

Each subject was studied after an 8 h fast and refrained from taking any medication or tobacco on the day of the investigation. Anterior imaging was used with a wide field of view gamma camera, linked to a Nodecrest Systems computer. The subjects were seated with the back of the chair reclined to 30° from the vertical. This allowed all of the small bowel to be included within the field of view of the gamma camera. The frame time was 1 min and the study duration 30 min. The test meal was 300 ml 15 per cent dextrose, labelled with 10 MBq ^{99m}Tc-diethylene triamine penta-acetic acid (DTPA). This was ingested at a standard rate of 50 ml/min with imaging commencing at the same time as ingestion.

Analysis of data

Following acquisition of the data onto hard disc, each study was corrected for movement using an image alignment technique which has recently been developed in our department. This will be described in greater technical detail elsewhere. Briefly, a computer program allowed a rectangular region of interest to be constructed around the gastric image on an early frame. Each subsequent frame was then displayed on the screen, identifying any movement of the gastric image (*Figure 1*). The gastric image was then moved back into the rectangle (*Figure 2*), thus ensuring that all gastric images were in alignment.

It has been recognized that following gastric surgery, a large proportion of a test meal may empty from the stomach during the ingestion period[4]. To estimate this fraction, at the end of the ingestion

Table 1 *Details of volunteers and patients undergoing gastric emptying studies*

	n	Male:female	Age (years) mean (range)	Drainage procedures	Time from vagotomy (years) mean (range)
Healthy volunteers	10	9:1	27 (20–39)	–	–
Truncal vagotomy without diarrhoea	14	10:4	47 (27–62)	13P, 1GE	5 ($\frac{3}{12}$–18)
Truncal vagotomy with diarrhoea	13	11:2	51 (41–72)	7P, 3GE, 3A	6 ($\frac{3}{12}$–19)

P, pyloroplasty; GE, gastroenterostomy; A, antrectomy

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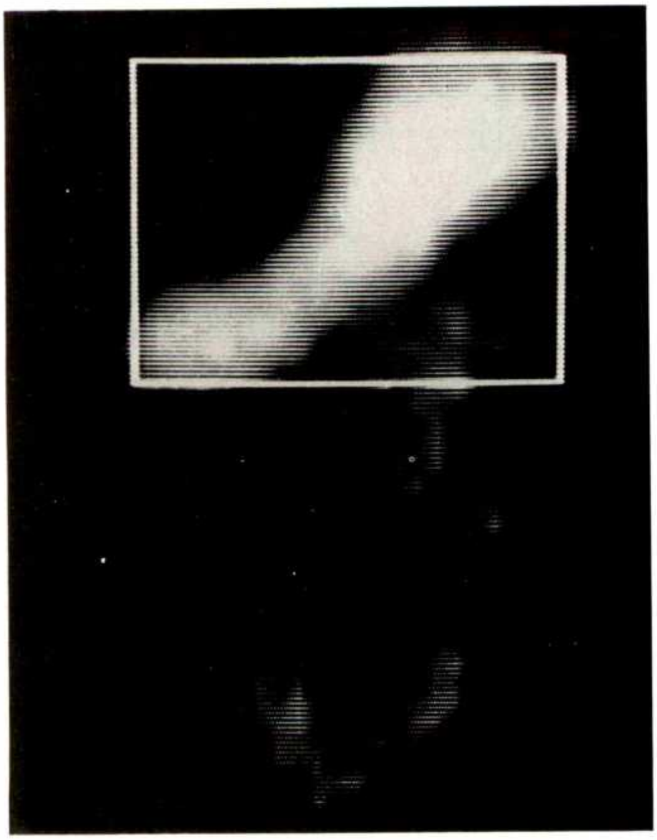

Figure 1 *Scintigraphic image from a study of a healthy volunteer. The 'box' region of interest allows for identification of subject movement*

period both gastric and small bowel regions of interest were plotted (*Figure 3*). The small bowel region so obtained contains scattered activity from isotope within the stomach. To correct for this a second large extragastric region was constructed, having a similar spatial relationship to the stomach as the small bowel region but containing no direct activity (*Figure 3*). The mean counts/cell in the latter region were subtracted from the mean counts/cell in the small bowel region, the result representing the true activity that had emptied into the small bowel during ingestion. Gastric counts at 6 min plus corrected small bowel counts at 6 min were taken to represent 100 per cent test meal activity, and gastric activity was plotted against this sum. Thus any shortfall in peak gastric activity below 100 per cent represents the percentage of the test meal having emptied during ingestion.

Finally, each gastric activity curve was corrected for decay of the isotope. On the basis of the results obtained we defined the initial phase of rapid gastric emptying as that occurring during the first 15 min following the start of test meal ingestion. To address the discrepancy between patient groups in terms of previous surgical procedures, the two subgroups of patients with TV + P were separately compared. Statistical comparisons were made by analysis of variance (all subjects), or Student's *t* test for unpaired data (patients).

Results

The mean gastric activity curves for healthy volunteers and for the groups of patients without and with diarrhoea are shown in *Figure 4*. The differences in gastric activity between the three groups were statistically significant throughout the study period. The rate of gastric emptying over the first 15 min was greater for patients without diarrhoea than for healthy volunteers ($P < 0{\cdot}001$), and this value was greater for patients with diarrhoea than for patients without diarrhoea ($P < 0{\cdot}001$).

Following this initial period, the rates of gastric emptying to the end of the study period were less in both of the vagotomized groups than in healthy volunteers ($P < 0{\cdot}001$). When comparing only patients who had previously undergone TV + P, values for gastric activity at 15 min remained significantly different (TV + P without diarrhoea $53 \pm 7{\cdot}7$ per cent, TV + P with diarrhoea $13 \pm 2{\cdot}3$ per cent, $P < 0{\cdot}01$).

Individual values of gastric activity at the end of the ingestion period are given in *Figure 5*. Only three patients with TV + D fell within the range from healthy volunteers. No patient with diarrhoea fell within the normal range.

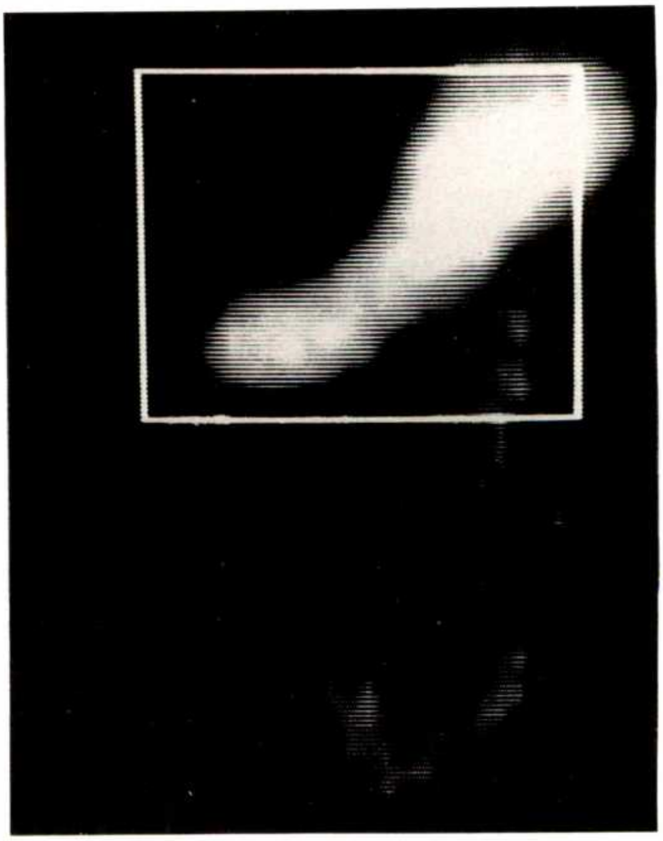

Figure 2 *The gastric image has been realigned with the 'box', correcting for movement*

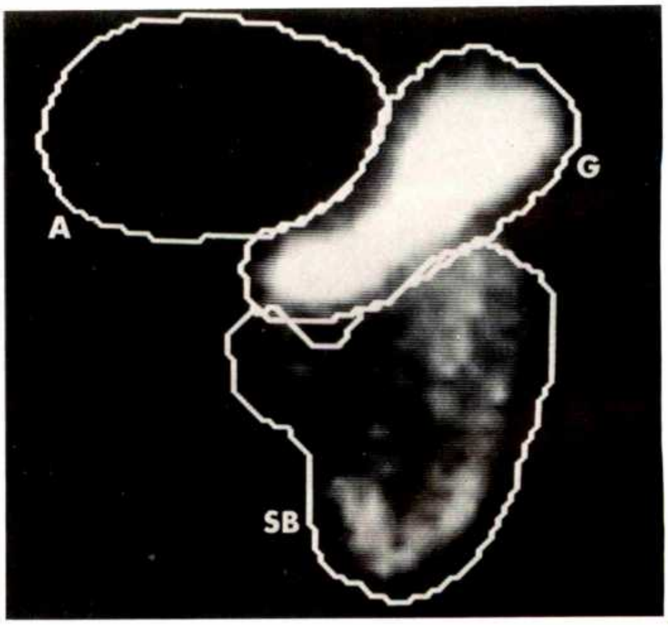

Figure 3 *Scintigraphic image at 6 min from a study of a patient with TV + D, showing the regions of interest which were drawn. G, gastric region; SB, small bowel region; A, second extragastric region, used to calculate the correction for scattered gastric activity. Note that there is already considerable activity within the small bowel*

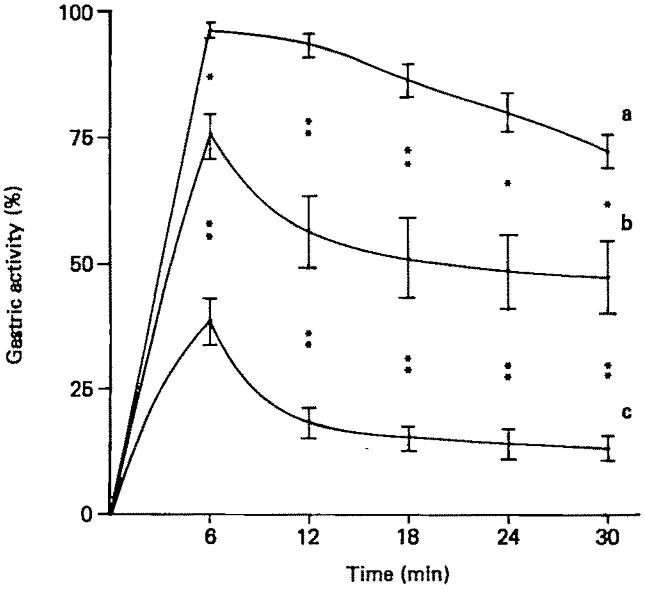

Figure 4 **a** *Gastric activity for healthy volunteers,* **b** *TV+D patients without diarrhoea, and* **c** *TV+D patients with diarrhoea plotted on a linear scale against time. Mean values at 1 min intervals are shown, with standard errors at 6 min intervals. Asterisks denote significant differences,* *$P<0\cdot01$; **$P<0\cdot001$ *ANOVA*

Discussion

The aetiology of postvagotomy diarrhoea remains uncertain. Truncal vagotomy with drainage is known to predispose to rapid initial gastric emptying. This is probably due to section of the vagal fibres responsible for gastric receptive relaxation[5] and also to a reduction in gastric outflow resistances caused by the drainage procedure[6]. A wide variety of other physiological disturbances occur following this procedure, several of which have been suggested as possible causes of diarrhoea. There could be excessive fluid shift into the intestine in patients with diarrhoea[3]. Phase III activity of the migrating motility complex returns prematurely in those with diarrhoea[7], perhaps transporting chyme into the colon before complete digestion and absorption can occur. Deranged small bowel motility could also predispose to bacterial colonization of the small bowel. Levels of distal small bowel peptides tend to be increased after ulcer surgery[8] and these might have effects on motility and secretion. Finally, abnormal delivery of bile to the small intestine interferes with fat digestion[9], and increased daily excretion of bile acids may stimulate water and electrolyte secretion by the colon[10].

Earlier studies, utilizing intubation techniques[11] or non-computerized gamma camera systems[2], found that initial gastric emptying was greater in vagotomized subjects with diarrhoea than in those without. This suggested that other physiological disturbances noted in patients with diarrhoea were merely a secondary result of excessive gastric emptying[7]. Surgery for postvagotomy diarrhoea has focused on delaying gastric emptying by either the reversal of drainage procedures[12] or the interposition of small bowel segments[13,14]. Using a computerized gamma camera system, a more recent study found rapid initial gastric emptying in vagotomized subjects both with and without diarrhoea, and the magnitude of this initial phase was similar in the two groups[3]. This suggested that patients with diarrhoea possessed a further abnormality which was responsible for generating this symptom, and that therapeutic efforts should be aimed at identifying and correcting any such defect.

In the present study 15 per cent dextrose was chosen as the test meal because it is unlikely to provoke symptoms when under the gamma camera[12], which can lead to premature abandonment of studies[15]. We believe that the method described for calculating emptying during ingestion is straightforward and probably more accurate than used in previous studies. The use of a computerized gamma camera system allowed more frequent measurement of gastric activity, thus giving a clearer description of gastric emptying patterns. Furthermore, the new image alignment technique enhanced the processing of data by providing a fairly rapid and simple correction for movement. We studied patients with a variety of drainage procedures, but there is no evidence to suggest that the pathogenesis of postvagotomy diarrhoea differs between drainage procedures. Patients with TV + P were also compared separately, and the difference in emptying between the groups with and without diarrhoea remained significant. The age of the control group was less than those of the patient groups. This is unlikely to have been of importance since gastric emptying has been reported to be slower in the elderly[16,17]. Although we did not test each patient for completeness of vagotomy, none had symptoms of recurrent ulceration or were being treated with H_2-blockers.

The results of this study support the concept that excessive initial gastric emptying is the primary factor in the pathogenesis of postvagotomy diarrhoea. However, there was some overlap between the vagotomized groups with and without diarrhoea, perhaps indicating individual differences in susceptibility to the development of diarrhoea. The exact pathogenesis of postvagotomy diarrhoea remains unclear. A rapid initial phase of emptying would appear to provoke secondary pathophysiological responses producing diarrhoea. Diarrhoea itself may occur after this initial rapid phase has ceased. Some subjects exhibited a clear initial rapid phase, yet only suffered from intermittent diarrhoea. Others have suggested that revisional surgery is less rewarding in this group[12]. In addition, the study confirms that many asymptomatic subjects have some degree of rapid early emptying following TV + D.

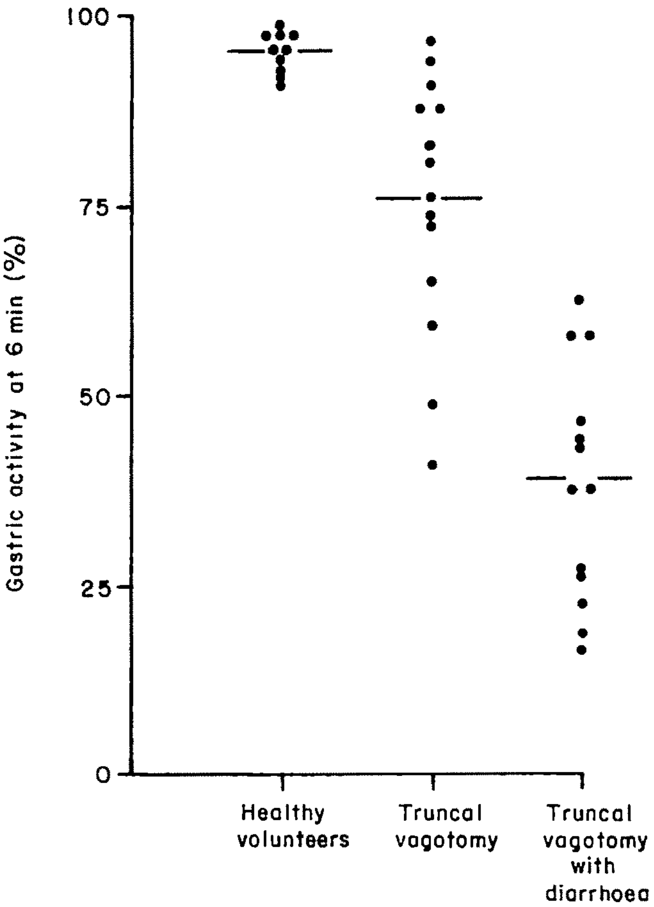

Figure 5 *Individual values of gastric activity at 6 min are shown for each of the three groups. Bars represent mean values*

This study clearly demonstrated that large quantities of a test meal may empty from the stomach over the ingestion period, emphasizing the importance of quantifying this fraction and of standardizing the ingestion period in gastric emptying studies. It showed that although gastric emptying of liquid may initially be rapid in subjects with TV + D, subsequent emptying may be slower than normal. Not infrequently these patients complain of a paradoxical combination of symptoms which are suggestive of both rapid gastric emptying and of gastric stasis. Previously stasis following truncal vagotomy has been attributed to deficient antral grinding of solids[5], but this study suggests that delayed gastric emptying of liquid could also contribute to this symptom.

Acknowledgements

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Announcement

The Association of Surgeons in Training

Membership of the Association is open to all Senior Registrars holding accredited posts in general surgery, urology, plastic surgery, neurosurgery, cardiothoracic surgery and paediatric surgery. Registrars in the above specialties who are 2 years post-fellowship may also apply. The Association represents the views of members on all matters relevant to surgical training besides having scientific and social functions.

If you are not a member please contact the secretary, Andrew McIrvine, 35 Elsie Road, Dulwich, London SE22 8DX, UK, for details of membership, local representatives and forthcoming meetings The next AGM will be held in Belfast on 8–10 September 1988.

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Bypass surgery for unresectable oesophageal cancer: early and late results in 124 cases

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The early and late results of bypass surgery in 124 patients with unresectable oesophageal cancer are reported. Patients were grouped according to the extent of disease: group A, tumour localized to the oesophagus where severe pulmonary disease contra-indicated oesophagectomy (n=9)*; group B, tumour* $\leqslant 10$ *cm in length with mediastinal invasion* (n=81)*; group C, tumour* > 10 *cm in length with mediastinal invasion and/or fixed malignant lymph nodes* (n=33)*. Extent of disease was not recorded in one patient. The operative mortality was 4 per cent but 9 other patients died in hospital (hospital mortality, 11 per cent). Mortality was increased in patients undergoing colon bypass and in those with a large tumour load but these differences failed to reach statistical significance. The most frequent complication was neck sepsis, secondary to leakage from the proximal end of the excluded oesophagus. Eighty-nine per cent of the survivors could eat a normal, unrestricted diet on discharge and eighty-two per cent of survivors had complete and lasting relief from dysphagia. Median survival after bypass was 5 months but survival was significantly improved by radiotherapy to the tumour* ($P < 0{\cdot}001$)*. Gastric bypass with radiotherapy is indicated in patients with extra-oesophageal spread of malignancy and in patients with tumours localized to the oesophagus who are unfit for resection. Bypass surgery may be contra-indicated in patients with a primary tumour* > 10 *cm in length and/or fixed lymph node metastases because mortality is increased and survival after operation is short.*

Keywords: Oesophageal carcinoma, bypass surgery, radiotherapy

Most patients with oesophageal cancer present when the tumour is advanced and incurable[1] so that the principal aim is to restore the ability to swallow. Many methods of palliation are in current use, including irradiation, chemotherapy, oesophageal bougienage and intubation, but the relief from dysphagia achieved by these methods is often incomplete and short-lived[1–4]. The role of bypass surgery in the management of advanced oesophageal cancer is controversial. Bypass operations can permanently restore normal swallowing but the patients are poor risks for major surgery and their survival may be measured in months. In this paper, the early and late results of bypass surgery in 124 cases of unresectable oesophageal cancer are reported. Factors associated with an increased risk of mortality have been examined and the influence of the extent of disease and chemoradiation therapy on survival after bypass surgery studied. An attempt has been made to identify patients who will obtain lasting benefit from bypass surgery and those in whom bypass operations may be contra-indicated.

Patients and methods

In a 7-year period ending November 1986, 559 patients with squamous carcinoma of the oesophagus were admitted to one of the five general surgical units at Baragwanath Hospital. Forty per cent of these cases underwent operation, either an oesophagectomy for potentially curable oesophageal cancer (101 patients) or bypass surgery for unresectable tumours (124 patients). Twenty-eight patients were admitted in a moribund state and died before any treatment could be given. Fifty-six patients with very large oesophago-airway fistulae who could not be made fit for bypass surgery underwent oesophageal intubation. The other 250 cases (45 per cent) were patients with advanced malignancy in whom bypass surgery was contra-indicated or who refused operation: 170 of these cases were entered into a prospective randomized trial to compare oesophageal intubation with dilatation plus bleomycin[5] and 80 patients were treated by radiotherapy and/or chemotherapy.

This report deals with the 93 men and 31 women aged from 22 to 77 years (mean age 51) who underwent an extrathoracic bypass operation.

After a detailed history and physical examination, every patient had a barium swallow, a chest radiograph, indirect laryngoscopy, oesophagoscopy and biopsy, bronchoscopy, routine haematological, serological and liver function tests and arterial blood gas analysis. Sonographic or computerized axial tomographic examination of the liver and coelic nodes was also performed. The diagnosis of squamous cell carcinoma of the oesophagus was confirmed histologically in all patients. Nine patients had T_2 and 115 T_3 tumours (TNM classification of malignant tumours, UICC, Geneva 1982). No patient underwent thoracotomy so the extent of disease was assessed by pre-operative investigations and from findings at laparotomy. Patients were then grouped, according to the extent of tumour load (*Table 1*): there were 9 patients in group A, 81 in group B and 33 in group C. Information was insufficient to determine extent of disease in one patient.

Indications for bypass surgery included signs of extra-oesophageal spread of malignancy into the airway or other mediastinal structures[6], primary tumours more than 10 cm in length, bronchoscopic signs of metastatic spread to tracheobronchial lymph nodes[7] and evidence of gross coeliac node involvement. A bypass operation was also performed for nine patients with tumours apparently localized to the oesophagus but where severe pulmonary disease contra-indicated oesophagectomy.

Pre-operative preparation

By the time of admission to hospital, 48 per cent of patients could only swallow liquids, 49 per cent had total dysphagia and 3 per cent were still able to eat soft food. Most patients had lost from 20 to 30 per cent of their body weight: the median pre-operative weight was 48 kg, and 21 per cent weighed < 38 kg. All patients underwent 2 weeks of intensive pre-operative preparation with some requiring up to 4 weeks to improve their nutritional and respiratory status. Nutritional support included a high protein, high calorie liquid diet: if the patient had any difficulty swallowing liquids, the malignant stricture was partially dilated to pass a fine-bore silastic tube into the stomach for enteral feeding. Eighteen patients with frank oesophago-airway fistulae were intravenously alimentated. Respiratory support consisted of chest physiotherapy,

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Table 1 *Extent of disease in patients undergoing bypass surgery for oesophageal cancer*

Group	Extent of disease
A	Tumour localized to oesophagus
B	Tumour $\leqslant 10$ cm in length with local extra-oesophageal spread (into airway, other mediastinal structures)
C	Tumour >10 cm in length with local extra-oesophageal spread and/or fixed malignant lymph nodes

training with an incentive spirometer and appropriate antibiotics for chest infections. Active pulmonary tuberculosis was excluded by sputum culture. Respiratory improvement was monitored by daily auscultation of the chest and repeated blood gas analysis.

Contra-indications to operation

Bypass surgery was contraindicated in patients with tumours <21 cm from the teeth, those with visceral metastases and those with large and/or fixed cervical node metastases occupying the area of the neck dissection. Contraindications to operation included continued weight loss and failure of the serum albumin to rise above 30 g/l despite intensive nutritional support. Any patient who was unable to co-operate with chest physiotherapy and clear the chest of purulent sputum as well as those with a P_{a,O_2} persistently <60 mmHg were excluded.

Operative techniques

The whole stomach[8] was used for the bypass in 116 cases. Eight patients with distal oesophageal cancers invading the stomach had an isoperistaltic colon bypass[8]. No patient underwent a thoracotomy and wherever possible the bypass was placed behind the sternum. The presternal route was used for high tumours and where scalene lymph node metastases were found at operation: continued tumour growth at these sites could compress a bypass in the narrow thoracic inlet and lead to recurrent dysphagia. A nasogastric tube, inserted at operation, was used to keep the bypass decompressed until postoperative ileus had resolved and then used for enteral feeding. After a barium swallow examination to exclude anastomotic leakage, the nasogastric tube was removed to allow the patients to take a liquid diet and, by the tenth postoperative day, soft food. A normal solid diet was given 12–14 days after surgery.

Operative mortality was defined as death within 30 days of operation. Hospital mortality includes all patients who died before discharge from hospital. Patients were followed up in the out-patient department: patients who failed to attend were followed by home visits. Patients who left Johannesburg and could not be contacted by letter or traced through friends and family were presumed dead from the date of the last follow-up.

Chemoradiation therapy

Radiotherapy was planned for all cases. However, 31 patients failed to return for this treatment or died before it was given. Ninety-three patients received radiation to the tumour in a dose of 5000 rad (68 cases) given over 4–6 weeks or 2000 rad (25 cases) in divided doses over one week. After reports that bleomycin may increase the effect of radiation therapy[9,10], 32 patients received bleomycin (five daily intramuscular injections of 30 mg) combined with the radiation therapy. A similar dose of bleomycin was administered to nine patients who refused radiotherapy

Statistical analysis

Contingency tables and survival curves were considered in the analysis of the data. In analysing the contingency tables either the χ^2 test or Fisher's exact test was employed depending on the cell frequencies. The survival curves were compared in a survival analysis utilizing the Breslow test.

Results

Mortality

The operative mortality was 4 per cent. Death was due to intra-abdominal sepsis (two cases) secondary to jejunostomy leakage and following reoperation for small intestinal obstruction, to septicaemia (two cases) after drainage of a subphrenic abscess and after breakdown of a colo-oesophageal anastomosis, and to hyperosmolar coma (one case) during intravenous alimentation.

Nine other patients died in hospital, 35–90 days after operation. These nine patients failed to recover from the complications of surgery, which included anastomotic fistulae (four cases), sepsis secondary to leakage from the excluded oesophagus (two cases) and pneumonia (three cases). The hospital mortality was 11 per cent (14/124).

Operative and hospital mortality rates were greater in patients who had a colon bypass compared with those who had a gastric bypass (*Table 2*) but these differences were not statistically significant. When the influence of extent of disease on mortality rates was examined (*Table 3*) it was evident that, as the extent of disease increased so did the risk of death after operation and before discharge from hospital. However the differences failed to achieve statistical significance.

Morbidity

The most common complication was neck sepsis, presenting either as purulent discharge from the cervical drain site (eight cases) or as an abscess appearing 2–4 weeks after operation (fifteen cases). Drainage of the neck abscess was followed by transient anastomotic leakage in seven patients. Three other patients also suffered transient leakage from the anastomosis. Anastomotic strictures developed in seven patients, secondary to neck sepsis (three cases), to reflux oesophagitis (two cases) and of unknown aetiology (two cases).

Chest infections occurred in 21 patients, one of whom had a lung abscess. Seven patients survived a second operation. The indications for reoperation included obstruction of feeding jejunostomy (two cases), delayed gastric emptying requiring revision of a pyloroplasty (two cases), drainage of a subphrenic abscess (two cases) and adhesive small bowel obstruction (one case).

The potentially lethal pneumonitis which was reported after radiation therapy combined with bleomycin in patients undergoing oesophagectomy[11] did not occur in this series. However one patient suffered transient sclerema of the hands and feet which was attributed to bleomycin.

Ability to swallow

Of the 110 survivors, 98 (89 per cent) could eat an unrestricted diet of roasted meat, maize and bread on discharge from hospital. Nine patients (8 per cent) were restricted to soft food (minced meat, mashed potatoes and maize porridge) and the functional result was not recorded in three others.

Eight patients, who had been eating normally, suffered recurrent dysphagia on follow-up. This was due to the late appearance of anastomotic fistulae (three cases), compression of a restrosternal bypass by malignant scalene nodes (two cases), delayed development of anastomotic strictures (two cases) and

Table 2 *Mortality in gastric and colon bypass surgery*

Bypass viscus	Colon	Stomach
Number of patients	8	116
Operative mortality	12·5%	3·4%
Hospital mortality	25%	10·3%

Mortality expressed as percentage of patients

Table 3 *Influence of extent of disease on mortality after bypass surgery*

	Group		
Extent of disease	A	B	C
Number of patients	9	81	33
Operative mortality	—	2·4%	9%
Hospital mortality	—	7·5%	18·2%

Extent of disease not recorded in one patient. Mortality expressed as percentage of patients

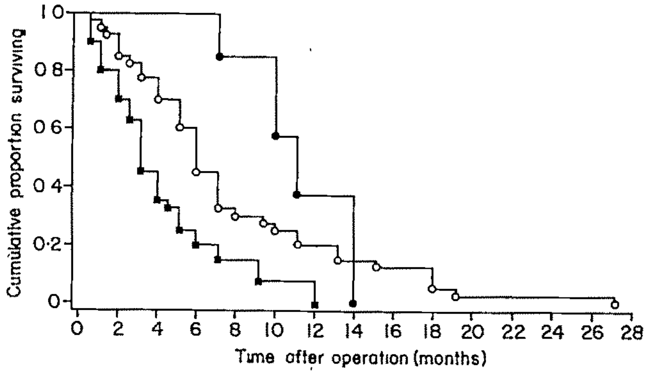

Figure 1 *The influence of extent of disease on survival after bypass surgery.* ●, *Group A (tumour localized to the oesophagus);* ○, *group B (locally advanced tumours),* ■, *group C (tumours > 10 cm in length and/or fixed malignant lymph nodes)*

invasion of the anastomosis in a presternal gastric bypass by paracardial node metastases (one case).

Ninety patients (73 per cent of all patients undergoing bypass surgery) had complete relief from dysphagia at the time of last follow-up.

Nutritional status

All patients lost weight in the immediate postoperative period despite enteral feeding. By 4–6 weeks after operation, 85 per cent of survivors had gained weight (from 2–10 kg) and strength which was usually maintained until relapse or dissemination of cancer became clinically evident, on average 3–4 weeks before death. Some 15 per cent of survivors, all of whom were group C patients, failed to gain weight and the general condition of these cases continued to deteriorate until they died.

Survival

The median survival for the group as a whole (including hospital deaths) was 5 months. Sixty patients survived for at least 6 months and sixteen patients for one year or more after the operation. Seven patients are still alive 3–14 months after surgery.

Extent of disease had a significant influence on survival. The median survival times were 10 months for group A, 6 months for group B and 3 months for group C and the survival curves (*Figure 1*) for all three groups were significantly different from each other ($P<0\cdot0019$). The survival curves (*Figure 2*) of patients receiving radiotherapy, irrespective of whether a 'curative' (5000 rad) or palliative (2000 rad) dose was administered, differed significantly ($P<0\cdot001$) from patients who did not receive radiotherapy. The survival curves of those who received radiotherapy alone and those who received radiation therapy combined with bleomycin did not differ significantly ($P<0\cdot9731$).

Discussion

It has been difficult to define the role of bypass surgery in the palliation of oesophageal cancer. Many methods are used to restore swallowing and the reported series of bypass operations have shown tremendous variation in results. Some small studies[12,13] report an operative mortality of < 10 per cent with normal swallowing restored in almost all patients but recent large series have reported mortality rates of 28–37 per cent[14,15]. This suggests that the results of bypass operations may depend more on the selection of patients than on the experience of the surgeons.

In the current series, the operative mortality of < 5 per cent is encouraging and can be attributed to intensive preparation of the patients with exclusion of patients who failed to improve. Hospital mortality rates, which included all patients dying in hospital are a more accurate index of the success of bypass surgery. The hospital mortality of 11 per cent in this study compares favourably with other series[14,15]. It is less than the mortality rate reported for palliative, incomplete resection[16,17]. In our experience, bypass surgery is a safer way to restore normal swallowing to patients with advanced tumours than palliative oesophagectomy[18].

Nevertheless, mortality in this series was unacceptably high in patients with very extensive tumours. Despite careful pre-operative preparation, 18 per cent of patients with primary tumours > 10 cm in length and/or fixed malignant lymph nodes failed to leave hospital alive. These patients should be offered safer methods of palliation and endoscopic intubation[19] or laser fulgarization of the tumour[20] may be appropriate for these cases.

There were many complications, the most frequent of which was neck sepsis. Despite pre-operative antibiotic prophylaxis, povidone-iodine irrigation of the oesophagus during operation and change of gloves and instruments after completion of the cervical anastomosis, 25 patients (20 per cent) suffered neck sepsis. This is a dangerous complication: in the series reported by Wong *et al.*[14] it was associated with a 90 per cent operative mortality rate. In this study, neck sepsis resulted in two hospital deaths, transient anastomotic leakage in seven cases and anastomotic strictures in three patients. The slow onset of the abscesses and the persistent purulent discharge from the cervical drain sites suggest that delayed leakage from the upper end of the bypassed oesophagus was the cause and this was identified by contrast studies in four cases. The problems associated with exclusion of the oesophagus have been reported[21] and various methods of closing the oesophagus have been tried. In an earlier series[22], the principal author (A.M.) advised dividing the cervical oesophagus 'as low as possible' to ensure that a good length of proximal oesophagus was available for the oesophago-fundic anastomosis. However, in six patients who have undergone bypass surgery since November 1986, the cervical oesophagus was divided above the level of the clavicle. It proved easier to close the distal oesophagus and to invert the suture line with a purse-string stitch. None of these patients has suffered neck sepsis or anastomotic leakage. This is now the preferred technique for closure of the excluded oesophagus.

In the current series, anastomotic leakage occurred in 9 per cent of patients undergoing gastric bypass and in 44 per cent of those who had a colon bypass. Other authors[16,23] report a high incidence of complications after colon bypass[18]. For these reasons, it is recommended that, when the stomach cannot be used for the bypass, an alternative to colon bypass should be considered for palliation of malignant dysphagia. Chronic aspiration from the obstructed oesophagus leads to small airway damage and loss of pulmonary tissue[24]; however, the mortality from pneumonia in the series was < 1 per cent which compares favourably with other reports[10,12].

Eighty-two per cent of survivors had complete and lasting relief from dysphagia after the bypass operation, comparing favourably with the results of oesophageal intubation in African

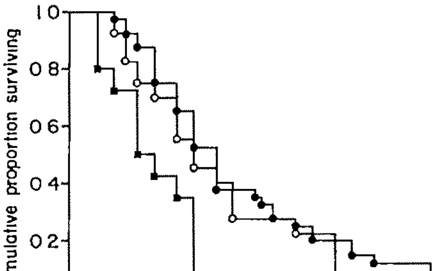

Figure 2 *The influence of radiotherapy on survival (hospital deaths excluded) after bypass surgery.* ■, *No radiotherapy;* ○, *palliative 2000 rad dose,* ●, *curative 5000 rad dose*

patients where <10 per cent of survivors eat normally[25] and 30 per cent suffer recurrent dysphagia. In the series reported by Watson[19] most patients had dysphagia for solids after both operative and endoscopic intubation. In another study of intubated patients[26], 44 per cent developed further dysphagia due to tube dysfunction and 37 per cent were readmitted for additional procedures to restore swallowing. Peroral dilatation of malignant strictures and laser fulgarization of intraluminal cancer can restore the oesophageal lumen, but both provide only temporary relief from dysphagia, and the benefits of dilatation decrease progressively with successive bougienage[3] and laser treatments have to be frequently repeated to maintain swallowing[20]. The results of radiotherapy for palliation of malignant dysphagia are disappointing: only one-third of patients with advanced oesophageal cancer will have lasting improvement in swallowing[27] and when an oesophageal cancer has invaded the tracheobronchial tree there is a grave risk that irradiation will precipitate or enlarge an oesophago-airway fistula, leaving the patient worse off than before[28]. It would appear that surgical reconstruction of the oesohpagus offers more certain relief from dysphagia than non-operative techniques of palliation[27].

In this series, survival was significantly influenced by irradiation of oesophageal cancers but there was no difference in the response to 'palliative' (2000 rad) compared to 'curative' (5000 rad) doses. The response of most tumours to radiation therapy is dose-dependent[27] so this was an unexpected finding. The failure of bleomycin to improve survival in this study confirms the results of other investigators[29]. Extent of disease had a significant influence on survival and it was encouraging to find that 18 per cent of patients with tumours apparently localized to the oesophagus or with locally advanced malignancies survived for at least 1 year after operation; however, the median survival of 3 months in those with a very large tumour load was disappointing.

Bypass surgery can give complete and lasting relief from malignant dysphagia to patients with unresectable oesophageal cancer; the stomach should be used as the bypass viscus in preference to the colon. The cervical oesophagus must be divided above the level of the clavicle so that the distal end can be securely closed. Gastric bypass and irradiation is the preferred method of palliation in the 30 per cent of patients with oesophageal cancer who have unresectable tumours and can be made fit for bypass surgery. While the combination of gastric bypass and irradiation results in a worthwhile period of good quality survival in those with locally advanced cancers, bypass surgery may be contra-indicated in patients with primary tumours >10 cm in length and/or fixed lymph node metastases. Hospital mortality rates are high and postoperative survival short in patients with a large tumour load.

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Autotransplantation of lingual thyroid into the neck

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Lingual thyroid is an uncommon developmental anomaly, and is the result of failure of the thyroid to descend from the foramen caecum to its prelaryngeal site. This may be the only functioning thyroid tissue in about $\frac{2}{3}$ to $\frac{3}{4}$ of patients[1,2]. The most popular treatment, presently, is transplantation or transposition of the lingual thyroid tissue into other sites[3–6].

Case report

A 9-year-old Saudi girl presented with a swelling on the posterior third of the tongue which she had been aware of for 6 years.

Clinical examination revealed a 5 × 5 cm mass on the dorsal surface of the posterior third of the tongue (*Figure 1*). No cervical thyroid was palpable. A provisional diagnosis of lingual thyroid was confirmed by ^{99m}Tc thyroid scan. The scan showed no evidence of further thyroid tissue. Her thyroid function tests were normal. Though her symptoms were mild, the unpredictability of follow-up made us advise surgical excision.

The lingual thyroid was exposed and excised through a transhyoid approach. Two slices of thyroid approximately 9 × 5 × 4 mm thick were then transplanted beneath the strap muscles. Eight thin slices of thyroid tissue were also implanted in the rectus abdominis muscles at different sites. She was intubated for 20 h postoperatively to allow oedema of the tongue to settle.

Six weeks later her thyroid function tests showed her T_3 was 0·5 (normal 0·8–2 μg/ml) and her T_4 1·7 (normal 4·2–11 μg/ml). Even though hypothyroid, she was clinically asymptomatic and no thyroid supplement was given. Four months later the thyroid scan showed uptake in the neck and abdomen and thyroid function tests were within the normal range. She was still euthyroid when seen in the outpatients clinic 6 weeks later.

Discussion

The incidence of lingual thyroid from post-mortem examination is approximately 10 per cent[1,7]. However, its occurrence from clinics of patients with thyroid disease is estimated[2] to be 1:3000.

Most lingual thyroids are asymptomatic. The most common symptoms are varying degrees of pharyngeal obstruction, cough, foreign body sensation, dysphagia, pain, referred pain (e.g. otalgia), haemorrhage or respiratory symptoms (e.g. dyspnea)[7–9]. Patients who are euthyroid and asymptomatic need to be observed, since the thyroid may fail to produce enough hormone for growth and development and they may later become symptomatic[8–10]. The symptomatic lingual thyroid should be totally excised; radio-iodine ablation has no place because of the risk to the gonads and the possible potential for inducing malignant change in the thyroid.

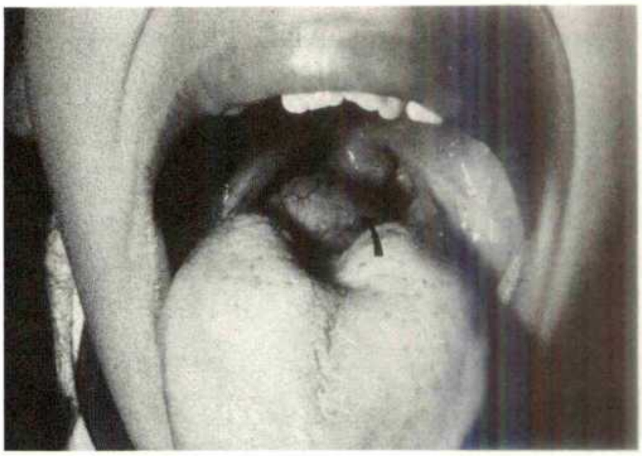

Figure 1 *The lingual thyroid.*

If cervical thyroid is also present, lingual thyroidectomy is curative. For a child with no cervical thyroid, autotransplantation is recommended, especially where replacement therapy would be unreliable.

The approaches favoured are transoral, lateral pharyngectomy and transhyoid. In the past tracheostomy was performed with lingual thyroidectomy but this is unnecessary since nasotracheal intubation for 24 h allows the lingual oedema to settle before extubation.

The rectus abdominis has been chosen for the transplant site most of the time because of its easy access. It seemed possible that through the transhyoid approach the thyroid tissue could be transplanted beneath the strap muscles, thus avoiding several incisions. However, as this has not been attempted before, we placed thyroid tissue into the rectus abdominis muscle as well. In the postoperative follow-up period thyroid supplementation should be avoided to allow the graft time to function under TSH stimulation. The result suggests that adequate function can be restored by placing thyroid slices in the neck without resort to an abdominal incision.

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Case report

Br. J. Surg. 1988, Vol. 75, March, 288

Omental abscess: a rare complication after implantation of autologous splenic tissue into the omentum

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Autotransplantation of the spleen can be undertaken in an attempt to preserve functional splenic tissue after splenectomy[1]. It is a procedure which is remarkably free of complications. Three cases of infection in autotransplanted splenic tissue which led to graft failure have now been reported. The possibility of sepsis in autotransplanted tissue should be borne in mind as a cause of persistent postoperative pyrexia and subsequent graft failure.

Case report

A 36-year-old alcoholic man with chronic relapsing pancreatitis underwent elective laparotomy. Drainage of a pancreatic pseudocyst, distal pancreatectomy and splenectomy with pancreaticojejunostomy were performed. Part of the spleen (about 20 per cent) was chopped into small fragments and these were placed in a pouch made from the greater omentum. The edges of this pouch were closed by interrupted Vicryl (Ethicon Ltd, UK) sutures. Six days postoperatively the patient became septicaemic. *Staphylococcus epidermidis* was grown from venous blood cultures and from the tip of a central feeding line. On the eleventh postoperative day the patient became acutely unwell with left upper quadrant abdominal pain and a pyrexia of 39°C. The white blood count was raised at 42×10^9/l. A CT scan (*Figure 1*) showed a collection of fluid and gas below the left diaphragm and an anterior homogenous mass in the omentum. Intravenous antibiotics were commenced and laparotomy confirmed three large omental abscesses and a resolving non-infected haematoma in the left subphrenic space. Histological examination of omental debris revealed 'active inflammation following autotransplantation of splenic tissue to the omentum.' Culture of pus obtained at the second laparotomy showed no growth but microscopy of the specimen was compatible with *S. epidermidis* colonization of the grafts. After drainage of the omental abscesses the patient made an uneventful recovery and was discharged home 2 weeks later.

Discussion

Infection of allografts in immunosuppressed patients is a well known problem[2]. In the case of autografts, however, infection is not a common complication, especially in vascularized grafts such as the kidney (G. Proud, unpublished results). Autotransplantation of tissues (rather than vascularized organs) such as parathyroid and pancreatic islets[3,4] has been undertaken without any reports of infection leading to graft failure. In autologous bone grafting, infection of the graft is rare but well recognized. The first case of infection following implantation of splenic tissue into the omentum was reported[5] in 1983. The second case of infection in a splenic implant was reported[6] in 1985 after a patient became septicaemic with *Salmonella 'San Diego'*. Experimental studies of splenic implants reveal that splenic tissue undergoes almost complete necrosis following implantation. This is followed by complete regeneration after 5 weeks[7]. Scintigraphy in man shows that functional tissue is present by the fourth week after implantation and increases in mass with time[5,8]. This sequence of necrosis followed by regeneration may lead to a period when the omental implant is little more than an ischaemic culture medium and susceptible to colonization by any organism which enters the circulation.

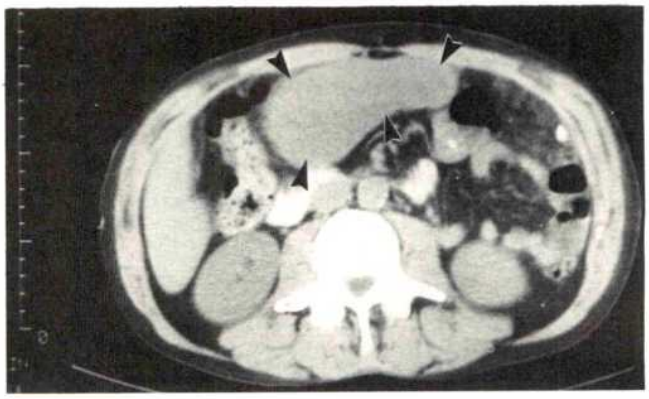

Figure 1 *CT scan of the abdomen showing omental abscess (arrowed) after splenic autotransplantation*

We advocate caution in tissue autotransplantation. While infection of autografts is infrequent our case suggests that care should be taken both to reduce the ischaemia in the implant and prevent systemic infection leading to colonization. We recommend that splenic fragments should be as small as possible (1–2 mm thick) and well dispersed, rather than contained in a localized pocket. Small implants should establish a blood supply more rapidly. Splenic implantation should probably be avoided when there is peritoneal or systemic sepsis. In the perioperative period, prophylactic antibiotics may be beneficial until the graft is vascularized.

Acknowledgements

Our thanks go to Mrs L. Kell for typing the manuscript.

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Case report

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Colitis cystica profunda of the rectum treated by mucosal sleeve resection and colo-anal pullthrough

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Colitis cystica profunda of the rectum is a rare condition, closely associated with 'solitary' rectal ulcer syndrome and rectal prolapse[1]. We report a florid case, successfully treated by mucosal sleeve resection and colo-anal pullthrough, a procedure not previously reported for this condition.

Case report

A 17-year-old man presented with a 4-month history of alternating constipation and diarrhoea, rectal bleeding, severe tenesmus and a prolapsing rectal mass, described by him as a 'bunch of grapes'. Sigmoidoscopy revealed an exuberant mass of rubbery polypoid tissue 2·5–10 cm from the anal verge. The lesion was almost circumferential, the only unaffected portion of the rectum being part of the left lateral wall.

Histological examination of extensive biopsy material revealed areas of mucosal ulceration with underlying granulation tissue containing haemosiderin deposits. The main feature was the presence of lakes of mucin surrounded by attenuated columnar epithelium, lying within the submucosa. A diagnosis of colitis cystica profunda was made.

The symptoms were sufficiently severe to merit surgical intervention. Complete local excision was carried out by submucosal sleeve resection of the entire rectal mucosa and tumour mass (*Figure 1*). This was achieved by a combined abdomino-anal approach, using submucosal injections of 1 in 200 000 adrenaline solution to facilitate dissection in this plane. The sigmoid colon was pulled through the denuded rectal muscular stump, and colo-anal anastomosis performed with 00 chromic catgut.

On review, 9 months after surgery, the patient remained free of symptoms, with a normal daily bowel action without straining, normal sensation and continence, and sigmoidoscopy to 20 cm was normal.

Discussion

This uncommon but increasingly recognized condition usually presents in the third and fourth decades. It appears in two forms, localized and diffuse, the localized form being more common in females[2], and occurring mainly in the sigmoid colon and rectum. The diffuse form occurs more frequently in males[3] and may affect the entire large bowel. Wayte and Helwig[4] in reviewing 24 cases found the disease localized to the rectum in 19 patients, and throughout the colon in the remaining 5 cases.

The pathogenesis of the disease is uncertain, but it is thought to be an acquired regenerative disorder following mucosal ulceration or fissuring. In the diffuse form, initiating factors include ulcerative colitis[3,4] or dysentery[4,5]. Traction on adenomatous polyps[6] or, more commonly, anterior wall prolapse occurring in 'solitary' rectal ulcer syndrome[1] predispose to the localized form. It has been reported following radiation-induced injury to the large bowel[7].

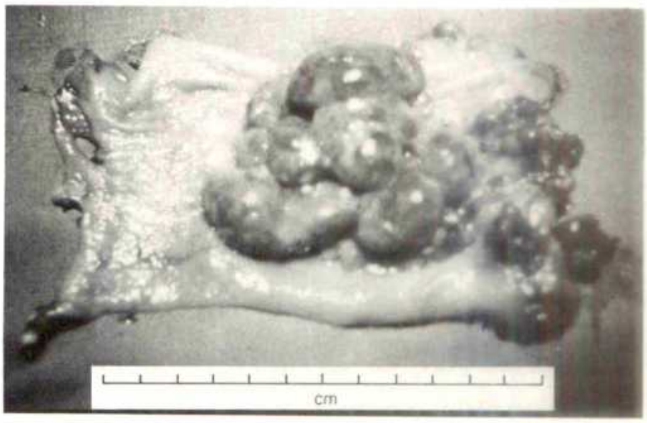

Figure 1 *Resected and opened specimen of the rectal mucosal sleeve. The distal (anal) end to the right is ragged from extensive peroperative biopsy*

It is important to distinguish the condition from invasive well-differentiated mucinous adenocarcinoma, with which it may be clinically and histopathologically confused[6,8,9], and which was initially considered in this patient before biopsy. In one series, reported by Green *et al.*[10], 7 of 51 patients were thought to have undergone 'needless' abdominoperineal excision of the rectum. Muto *et al.*[6] and Quizilbash *et al.*[8] emphasized the significance of haemosiderin deposits in support of the diagnosis of misplaced epithelium, rather than invasive cancer.

Local excision is widely advocated, although the results have not been universally favourable[2]. Local fulguration, although not widely reported, would also appear to produce disappointing results[11]. Only resection of the affected segment of bowel seems uniformly effective[2].

Circumferential disease in the rectum has in the past precluded local excision[2], and the severity of symptoms led us to consider abdominoperineal excision of the rectum. Instead, mucosal sleeve resection was carried out without specific antiprolapse measures. The potential risk of leaving misplaced islands of mucosal epithelium could lead to recurrence; however, the complete relief of symptoms in our patient should encourage further evaluation and long-term follow-up of the procedure.

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Correspondence

Staphylococcal infection of open granulating wounds

Authors' reply

Sir

In their comments and queries about our findings, Dr Eykyn and Professor Phillips (*Br J Surg* 1987; **74**: 1067) are discussing a problem different from the one addressed in our paper (*Br J Surg* 1987; **74**: 95–7). Their concern is clearly with pre-operative and early postoperative bacteriology. Ours is with ambulant patients attending a granulating wound clinic. We now recognize that the exact nature of the clinic was not detailed in the paper and regret this omission. It is fairly widely known that the clinic has been in existence for 15 years and sees 400 new granulating wounds each year—many from outside Cardiff and some from all over Britain.

We have no control over the primary treatment of many of these cases, a situation similar to that of any clinic facing the problems of an established granulating wound. Hence we are not considering questions such as the role of anaerobes in the pre-operative infections associated with axillary hidradenitis—where we have no difficulty in isolating these bacteria, fastidious or otherwise. However, anaerobes quickly disappear after the appropriately wide excision of affected skin which we practise. In 80 such excisions studied to date our wound clinic has never found them responsible for a postoperative infection. The other observations of Eykyn and Phillips similarly lack relevance to infection in mature open granulating wounds and to the significance of staphylococci found in them. We have considered the role of these and other organisms in more detail in a previous study of pilonidal sinus excisions healing by open granulation[1]. In that series there was one example of disease in a deep wound due solely to staphylococci but it is the only one we have met in more than 400 such excisions studied bacteriologically. Last month we met a possibly similar infection in an abdominal wound for the first time, but our advice remains to treat clinical infections of a deep open wound ostensibly due to staphylococci also for anaerobic infection and to seek improvement in drainage. In the absence of clinical infection isolations of *Staphylococcus aureus* should be ignored.

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1. Marks J, Harding KG, Hughes LE, Ribeiro CD. Pilonidal sinus excision—healing by open granulation. *Br J Surg* 1985; **72**: 637–40.

Parietal cell vagotomy

Sir

The report by H.-E. Jensen and his colleagues, from the Kommunehospitalet, Copenhagen (*Br J Surg* 1987; **74**: 1056–9), that 30 per cent of patients developed recurrent ulceration on follow-up of 14–18 years after parietal cell vagotomy (PCV), is disturbing. Nevertheless, for several reasons, I do not believe that we should conclude that the recurrence rate after PCV is necessarily 30 per cent.

Not all the patients operated on were suffering from duodenal ulceration. Some had prepyloric or pyloric ulcers and we are not told how many. There is by now a great deal of evidence that the incidence of recurrent ulceration after PCV for such ulcers is much higher than the incidence of recurrent ulceration after PCV for duodenal ulceration. For example, in a recent paper[1], Paul Jordan reported that the incidence of recurrent ulceration after PCV performed for duodenal, pyloric and prepyloric ulceration was 10 per cent in the long-term, but that when patients with duodenal ulcer alone were considered, the incidence of recurrent ulceration was only 6 per cent. Admittedly, Jensen and his colleagues noted no difference in recurrence rates when PCV was used for duodenal ulceration compared with pyloric/prepyloric ulceration, but one would presume that the numbers of patients with pyloric/prepyloric ulceration were relatively small and thus the study may not have had the power to demonstrate differences which in truth exist.

A similar comment would apply to the authors' comment that there was no difference in recurrence rates when the operation was performed by a consultant or by a registrar. About 70 per cent of the patients were treated by registrars.

Jensen *et al.* do not state how many surgeons were actually involved in their series, but it should surely be emphasized that there is a large intersurgeon variation in recurrence rates after parietal cell/highly selective vagotomy. We have commented that some surgeons in our department had recurrence rates of 2–5 per cent after 5–10 years follow-up, whereas other surgeons had recurrence rates of 20–30 per cent after similar lengths of follow-up. However, the best example of this intersurgeon variation is reported by Adami and colleagues[2], who reported that one surgeon had a 46 per cent recurrence rate at 8 years follow-up, while others had only 6 per cent recurrence.

The implication both in the paper by Jensen *et al.* and in the leading article by T.V. Taylor (*Br J Surg* 1987; **74**: 971–2) on PCV, is that incidences of recurrent ulceration after PCV are greater than incidences of recurrent ulceration after truncal vagotomy. It would be surprising if this were true, because both types of vagotomy reduce acid output by similar degrees in the long-term, and both are followed by similar elevations of serum gastrin. There is no reason to believe that the defence mechanisms of the gastric and duodenal mucosa are damaged more by PCV than by truncal vagotomy. Besides, careful, prospective, randomized trials in Aberdeen[3] and Sheffield[4] showed similar incidences of recurrent ulceration after these two types of vagotomy.

Finally, I would like to point out that, from Houston, Paul Jordan reported after 10 years' follow-up of patients after PCV or selective vagotomy with antrectomy that the incidence of recurrent ulceration after PCV was not significantly higher than the incidence of recurrent ulceration after selective vagotomy with antrectomy. The incidence of recurrent ulceration after PCV for duodenal ulcers in Jordan's series was only 6 per cent. At the Leeds General Infirmary, the incidence of recurrent ulceration after highly selective vagotomy in my own personal series of patients treated between 1969 and 1974 was 2 per cent at 5 years and approximately 5 per cent at 10 years. Likewise, Matheson and his colleagues in Aberdeen have now followed up the patients in their prospective trial of highly selective vagotomy *versus* truncal vagotomy plus pyloroplasty for duodenal ulcer and have found that only 5 per cent of patients had developed recurrent ulceration 10–12 years after highly selective vagotomy[5]. These findings, in carefully conducted prospective studies, are certainly at variance with those of Jensen *et al.* because we now have a maximum follow-up of nearly 19 years in Leeds and there is very little evidence of recurrence developing after 11 years in our series here. In conclusion therefore it should not be accepted that, as a general rule, the incidence of recurrent ulceration after PCV is as high as 30 per cent.

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Authors' reply

Sir

We thank Professor Johnston for his erudite comments on our paper. We fully appreciate why he finds our results 'disturbing'. Our department too, having cradled, nurtured and fostered parietal cell vagotomy (PCV) for 18 years, was deeply disturbed and sorely disappointed.

We are unable to explain the difference between our results and those of Professor Johnston. We do not believe this is because of differences in our ability to achieve an adequate vagotomy. The earlier results of this series of patients which have been published many times previously demonstrated the effectiveness of our vagotomy procedure. All our patients had at least one and often two different intra-operative tests of completeness of vagotomy. All the patients had pre- and postoperative insulin tests at 3 months and 5 years after surgery. Results of the insulin tests showed a 90 per cent reduction of acid secretion at 3 months and an

84 per cent reduction at 5 years. In all, 64 per cent of the insulin tests were negative by Hollander's criteria. These figures are similar to, or better than, those achieved in other PCV trials[1–4].

Professor Johnston quotes that recurrence rates after PCV vary between 2 per cent and 46 per cent in the hands of different surgeons. We are aware of this surgeon variation and have previously reported that one of us (H.-E.J.) had much better results than other surgeons in the department[5]. Although this tendency persisted in the current report, it did not reach statistical significance.

We believe that the single most important message to emerge from this study is that the recurrence rate after PCV increases with time. We saw recurrent ulcers as late as 16 years after operation. A total of 40 per cent of our recurrences occurred after 10 years. We too have reported low recurrence rates early after surgery. We question therefore Professor Johnston's comparison of our high recurrence rate, at a mean of 15·5 years after surgery, with the low rates of others after follow-up durations of about 10 years. Extrapolating from our data, these surgeons can expect a continuous rise in their recurrence rates. While their rates may never reach 30 per cent, they may yet approach unacceptably high levels if followed for long enough.

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1 Kragelund E, Amdrup E, Jensen H-E. Qualitative and quantitative differences in the response of the stomach to pentapeptide and insulin secretory stimulation at 2–3 months follow-up after parietal cell mass vagotomy. *Ann Surg* 1972; **176**: 656–8.
2. Amdrup E, Jensen H-E, Johnston D, Walker BE, Goligher JC. Clinical results of parietal cell vagotomy (highly selective vagotomy) two to four years after operation. *Ann Surg* 1974; **180**: 279–84.
3. Jensen H-E, Amdrup E. Follow-up of 100 patients five to eight years after parietal cell vagotomy. *World J Surg* 1978; **2**: 525–32.
4 Jensen H-E, Kjaergaard J, Meisner S Ulcer recurrence two to twelve years after parietal cell vagotomy for duodenal ulcer *Surgery* 1983; **94**. 802–6.
5. Hoffmann J, Jensen H-E, Schulze S, Poulsen PE, Christiansen J. Prospective controlled vagotomy trial for duodenal ulcer: results after five years. *Br J Surg* 1984; **71**· 582–5.

Author's reply

Sir

I would agree that all recurrence rates after highly selective vagotomy are not so disappointing as those reported by Jensen and his colleagues. The rates reported by Johnston and by Matheson on British patients are much more acceptable and, in view of the virtual indemnity that can be given against dumping and severe diarrhoea, this operation, or one closely related to it, must still be the first choice in elective ulcer surgery It is possible that ulcers in Scandanavia run a more aggressive course than those in Britain. Should this be so, it is still important to note that none of the patients in Jensen's series who developed a recurrent ulcer either bled or perforated from this and thus potential ulcer mortality was completely overcome over this 14–18-year period. Mortality is a factor often forgotten in the heated arguments which prevail regarding short-term ulcer healing, but it stands at 4500 per annum in England and Wales and is rising.

The point which I wished to emphasize most strongly in my leading article, on long-term results following highly selective vagotomy, was that of those who developed a recurrence 40 per cent did so after more than 10 years. This would suggest that a factor other than return of acid secretion is responsible. Even the most indolent and lethargic of sprouting or regenerating nerves would be expected to have achieved its full growth potential by 5 let alone 10, 15 or even more years. Any hormonal changes, however subtle, would likewise have been expected to wreak their effect on the unsuspecting mucosa long before these periods of time. This factor may well be related to pyloric, antral or gastric motor function which like all muscular physiology deteriorates with time following denervation. For example the incontinence which follows pudendal nerve damage may take years to manifest itself. This may be a reason for adding pyloroplasty to highly selective vagotomy or alternatively treating the recurrent ulcer by endoscopic pyloric dilatation. The Shay rat model has brought testimony to generations of physiologists that impaired pyloric function or gastric emptying is a powerful ulcerogenic stimulus by a mechanism which is not fully understood.

Such a hypothesis would take years to prove and the scientific data are not available as few such long-term studies exist. The largest and longest followed up series of ulcer patients reported in the literature is that of the Edinburgh Western General Hospital described by Small[1] Long-term complicated recurrences were not encountered in these 779 patients treated by either gastrectomy or vagotomy and drainage between 1947 and 1965.

I would agree with Professor Johnston that highly selective vagotomy, or a closely related procedure, is the best option for elective ulcer surgical treatment, but preservation of the hepatic branches of the anterior vagus and the coeliac branches of the posterior trunk will probably allow pyloroplasty to be performed without dumping or diarrhoea and perhaps we should not condemn it too hastily on purist grounds. Perhaps, the process of evolution in peptic ulcer surgery has not stopped with pylorus preserving highly selective vagotomy. We seem to have reached another crossroads in ulcer surgery

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1. McLean Ross AH, Smith MA, Anderson JR, Small WP. Late mortality after surgery for peptic ulcer. *New Engl J Med* 1982; **307**. 519–22.

Sodium nitroprusside induced hypotensive anaesthesia for reducing blood loss in patients undergoing lienorenal shunts for portal hypertension

Sir

In the interesting paper by Sood *et al.* (*Br J Surg* 1987; **74**· 1036–8) the authors do not mention the potential risk to the brain of any form of hypotensive anaesthesia including that induced by sodium nitroprusside. This agent is both a cerebral vasodilator and impairs cerebral autoregulation with the potential for infarction in the watershed areas of the brain Provided mean arterial blood pressure in a previously normotensive patient is kept above 50–60 mmHg then the net effect of sodium nitroprusside on the cerebral circulation should be maintainance of cerebral blood flow within the normal range However, should the blood pressure fall below that level intra-operatively, cerebral ischaemia may result Furthermore, the threshold at which this occurs will almost certainly be higher in patients who were hypertensive pre-operatively.

What level of hypotension is safe in patients of different ages, different levels of pre-operative blood pressure and with different systemic diseases such as portal systemic encephalopathy? This has not been resolved The neurological sequelae may not always present as gross neurological disability and careful comparison of pre- and postoperative neuropsychological assessment and every day functioning is required as has been learned in the study of the cerebral effects of cardiopulmonary bypass.

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Management of periampullary carcinoma

Sir

We read with interest the recent papers on the management of periampullary carcinoma (*Br J Surg* 1987, **74**. 916–19 and 957–61). They support our contention that the results of radical resections are better if performed in referral centres We would be most interested to know the problems Mr Robertson *et al.* encountered in association with local resection, other than the two deaths recorded The actuarial survival curves would appear to support both our views and those implied by the authors—namely that local resection merits further study. However we must be wary of drawing firm conclusions from life-table analyses involving small numbers of patients reviewed at lengthy time intervals[1].

Mr J.P Neoptolemos and his colleagues state that the case for local resection has to be made This is so in their series in which only four cases had a local resection. However, if the two operations have a similar 5-year survival[2] there can be little doubt as to which is less traumatic to the patient.

We feel there is enough evidence to warrant a prospective study of local resection. With the aid of endoscopic retrograde cholangiopancreatography and careful histological grading a more accurate definition of the role of local resection should emerge. Finally, all three studies appear to show that bypass surgery has no part to play in the management of these lesions.

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1. Underwood CJ, Faragher EB The uses and abuses of life-table methods in vascular surgery *Br J Surg* 1984, 71: 495–8.
2. Knox RA, Kingston RD. Carcinoma of the ampulla of Vater *Br J Surg* 1986; 73: 72–3.

Authors' reply

Sir

It is good to have an opportunity to comment on the letter by Mr Knox and Mr Kingston. We are strongly of the belief that radical resection should be performed in specific specialist referral centres. In answer to the question regarding the six surviving patients with locally resected ampullary carcinoma in our own series (*Br J Surg* 1987, 74: 816–19) three developed recurrent carcinoma from which they died. This is a higher incidence than was found in their study in which just under 25 per cent of patients similarly treated developed recurrence[1], but similar to the figure of just under 50 per cent in another British paper[2] As the numbers in the world literature are still too small, it is difficult to delineate clearly the place of local resection as many of the papers are based on retrospective studies and it is impossible to ascertain whether or not the smaller tumours were chosen for local resection and larger lesions for more radical resection. As has been highlighted by another recent study (*Br J Surg* 1987, 74 957–61) not all the lesions are macroscopically or microscopically the same so that we tend to be trying to compare apples with oranges

While theoretically a prospective study of local resection against radical resection is attractive there are considerable logistic problems with a tumour of such rarity, but it may be possible to mount this on a national basis

Disagreement is inevitable with the concluding statement in the letter by the Manchester surgeons as in our experience bypass surgery has been virtually only used in patients with disseminated disease, or very locally advanced disease in a patient considered unfit for resection; we would believe that bypass surgery still has a place to play in management, although endoscopic stenting may well have superseded it already

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1. Knox RA, Kingston RD Carcinoma of the ampulla of Vater. *Br J Surg* 1986; 73: 72–3.
2. Newman RJ, Pittam MR. *J R Coll Surg Edinb* 1982; 27. 154–7.

Aorto-enteric fistula

Sir

The case report by Williams, Charlesworth and Jones (*Br J Surg* 1987, 87: 645–6) contains the *ex cathedra* statement that aorto-enteric fistula may occur when the graft is not covered by peritoneum. This widely held and always unsubstantiated belief is not made more credible by frequent repetition.

In an elegant experimental study Busuttil *et al.*[1] demonstrated that excluding peritoneal covering of aortic graft anastomoses did not produce aorto-enteric fistulae. Fistulae were produced by deliberately creating false aneurysms and by the intravenous infusion of *Staphylococcus aureus*

It is customary to teach vascular surgical trainees that the posterior peritoneum must always be closed over an aortic graft to prevent aorto-enteric fistula formation This dictum is illogical since most fistulae occur into the duodenum and this structure being retroperitoneal will not be covered by peritoneum at its point of contact with the aortic anastomoses.

Prevention of aorto-enteric fistulae depends on secure anastomoses to avoid false aneurysms and aseptic technique with peroperative antibiotic prophylaxis to discourage infection The peritoneum over an aortic graft, as elsewhere in the abdomen, can confidently be left to close itself.

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1. Busuttil RW, Rees W, Baker JD. Pathogenesis of aortoduodenal fistula experimental and clinical correlates. *Surgery* 1979; 85· 1–13.

Urethral versus suprapubic catheterization

Sir

We would like to endorse the recommendation of Mr Sethia and his colleagues from Oxford who have noted the superiority of suprapubic catheterization of the bladder to the per urethral route in patients who require urinary drainage during and after abdominal surgery (*Br J Surg* 1987; 74 624–5). Their findings reflect a similar experience of our own when we reviewed the urological complications of colorectal surgery in the Section of Surgery at the Royal Society of Medicine (4 February 1987).

The Oxford experience is predominantly colorectal and like us they found an alarmingly high urinary infection rate with urethral catheterization despite appropriate antibiotic prophylaxis. We use metronidazole and cefuroxime and found that of 99 patients catheterized by the per urethral route 28 (28 per cent) developed a urinary infection whereas only 2 of 22 patients (9 per cent) with suprapubic catheters developed this complication. We also used the 10^5 colony forming units per ml of urine from a catheter specimen as a criterion for a significant urinary infection.

It has been our policy for several years to relieve acute retention of urine with a fine bore suprapubic catheter Leakage around the catheter has not been a problem and with recent modifications in design at abdominal wall level we have found the 14G pigtail Teflon® catheter to suit most of our requirements Despite the cost differential to latex Foley catheters, we feel the regular use of one type of suprapubic catheter by junior surgical staff and nurses has made the suprapubic route preferable to patients and staff alike.

Although catheter related urinary sepsis is the most frequent complication of urethral catheterization urethral tears, strictures, periurethral abscess and urethral pain should be considered also Suprapubic catheterization of the urinary bladder is easy to perform, easy to manage postoperatively, and tolerated well by patients We agree that even with vigorous urethral catheter care the results of suprapubic catheterization are hard to match on a general surgical ward where a wide range of surgery is undertaken.

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Sir

We read with interest the article by Sethia *et al.* (*Br J Surg* 1987; 74: 624–5) concerning the use of suprapubic catheters in preference to urethral catheters in patients undergoing general surgical procedures. The marked reduction in urinary tract infection when using suprapubic catheterization exactly reflects our own experience with an almost identical regime using latex Foley catheters inserted operatively at laparotomy.

Of even greater significance, perhaps, is the avoidance of urethral stricture when using the suprapubic route. It is well known that urethral catheterization predisposes to stricture formation[1], particularly if a latex catheter is used[2]

In the few cases where suprapubic catheterization is not feasible we use a silastic urethral catheter and remove this as soon as possible. The use of latex in the urethra seems wholly inappropriate, bearing in mind the inflammatory fistula produced by the latex T tube in biliary surgery.

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1. Blacklock NJ Catheters and urethral strictures. *Br J Urol* 1986, 58. 475–8.
2. Keitsen WA, Abreu A, Navarro I, Bernreuter E, Allen JS. Urethral strictures: prevention with plastic indwelling catheters. *J Urol* 1986; 99: 187–8

Percutaneous oxygen tension

Sir

I read with interest the article by Mr Stacey *et al.* on changes in the apparently normal limb in unilateral venous ulceration (*Br J Surg* 1987; **74**: 936–9). However, I must take issue with both the method of measurement of percutaneous oxygen tension and the interpretation of the results which imply that a low cutaneous oxygen tension reflects poor diffusion of oxygen from the capillaries. Most equipment used for percutaneous oxygen measurement is designed for use in neonates who have very thin skin and can give unreliable results when used in adults[1]

The actual measured oxygen tension will be a function of the amount of blood flowing into the limb, the amount of blood leaving the limb and the skin thickness. In a limb with already diseased venous circulation and a defective pump mechanism as stated in the paper, venous pooling and increased oxygen dissociation may allow for a lower measured oxygen tension. Defective arterial inflow into the limb will also give low readings and although the authors state that ankle:brachial ratios were measured, no reference to this is made in interpretation of the measured results.

In the evaluation of identical equipment I found that more reliable information was gained by having the patients breathe 100 per cent oxygen for 5 min. The gradient of the increase in oxygen tension in the limb compared with the gradient at the sternal ankle was measured rather than a static value. This method may give differing results from those obtained in the study particularly if arterial insufficiency is excluded

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1. Spence VA, McCollum PT. Evaluation of the ischaemic limb by transcutaneous oxymetry. Greenhalgh RM, ed *Diagnostic Techniques and Assessment Procedures in Vascular Surgery.* London: Grune and Stratton, 1975.

Authors' reply

Sir

Mr Holdsworth's letter highlights some of the difficulties in interpreting the P_{tc,O_2} results obtained by the transcutaneous oxygen electrode. As he correctly states, it is dependent upon blood flow, central oxygenation, tissue thickness and tissue diffusion There are numerous different measures which can be shown to influence results, including the temperature of the electrode[1], raising and lowering the limbs[2], and breathing oxygen[3].

Unfortunately, he seems to have missed the point that these limbs had markedly different P_{tc,O_2} to a group of matched control subjects lying at rest. These limbs were not ischaemic—they all had ankle: brachial Doppler arterial pressure ratios > 0·95 We have performed the measurements breathing oxygen and the difference remains true, although the baseline for both groups moves up.

When it comes to interpreting the results it is much more difficult to do so with certainty; however, we have presented data, at the Vascular Surgical Society meeting in Newcastle upon Tyne in November 1987, to show that the P_{tc,O_2} ratio correlates with the extent of pericapillary fibrin deposition in the dermis. This encourages us to think that our interpretation may be correct. Does Mr Holdsworth have a better explanation for our data?

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1. Mani R, Gorman FW, White JE. Transcutaneous measurements of oxygen tension at edges of leg ulcers. preliminary communication *J R Soc Med* 1986; **79**: 650–4.
2. Clyne CAC, Ramsden WH, Chant ADB, Webster JHH. Oxygen tension on the skin of the gaiter area of limbs with venous disease. *Br J Surg* 1985; **72**: 644–7.
3. Gilliland EL, Llewellyn CD, Cornwall JV, Goldie B, Gerber C, Lewis JD. Transcutaneous oxygen values surrounding venous ulcers—field changes and response to inhaled oxygen. *Br J Surg* 1986; **73**: 1039.

Synchronous colorectal carcinomas

Sir

We read with interest the article on synchronous colorectal carcinomas by Finan (*Br J Surg* 1987; **74**: 945–7). This prompted us to review our own experience in a general hospital.

Over a 4-year period (July 1983–June 1987), 147 patients were admitted with colorectal cancer. Six (4·1 per cent) patients had a synchronous tumour and 1 (0·7 per cent) patient had an early metachronous lesion (<3 years from initial surgery). The site, Dukes' classification, and when the second tumours were detected are shown in the *Table*.

Patient number	Site (first tumour second tumour)	Dukes' classification	Detection
1	Sigmoid	C	
	Caecum	C	Operation
2	Left colon	C	
	Caecum	C	Pre-operative
3	Left colon	C	
	Sigmoid	A	Operation
4	Right colon	C	
	Sigmoid	B	Pathological examination
5	Sigmoid	C	
	Left colon	B	Operation
6	Caecum	C	
	Left colon	C	Operation
7	Left colon	A	
	Rectum	C	Metachronous

In one patient who had a panproctocolectomy for ulcerative colitis, the synchronous tumour was found at pathological examination One other patient had a sigmoid resection and presented 32 months later with a small polypoidal lesion in the rectum despite sigmoidoscopic surveillance. Our overall experience seems largely to reflect Finan's much larger series though only two out of seven patients had a better Dukes' classification in the second tumour. We agree that full colonic examination is essential in practice, where possible. However one must balance the risks of the suggested colonoscopic examination pre- or peroperatively against the very low missed pick-up rate of synchronous tumours by manual examination, particularly in the case of the obstructed colon: bowel preparation may not be possible, on-table colonic lavage may not be practised in the centre concerned, and the extra time to perform the procedure especially in the ill patient would be difficult to justify. Whether the presence of 'missed' synchronous tumours influences the prognosis and survival rate remains to be seen. If one speculates that it falls into the category of recurrent disease prognosis, Tornqvist has suggested that even with aggressive follow-up to detect early recurrence there is little or no effect on long-term survival[1]

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1. Tornqvist A, Ekelund G, Leander L. Value of intensive follow-up after curative resection for colorectal carcinoma. *Br J Surg* 1982; **69**: 725–8.

Pain scores in haemorrhoidectomy

Sir

We feel compelled to comment on the use of pain scores in the paper by Roe *et al.* in the October edition of the Journal (*Br J Surg* 1987, **74**: 948–51) comparing two techniques of haemorrhoidectomy The pain charts illustrated are not visual analogue scales, but categorical in nature and therefore give different information from visual analogue scores. Comparison with other studies using visual analogue scores is consequently not possible.

As a patient's impressions of treatment are realized to be of increasing importance, it is essential that both objective physiological and validated psychometric tests are used. Methods of psychometric comparison are well documented[1,2] The true worth of the alternative techniques of haemorrhoidectomy would have been better elucidated had the same degree of effort been applied to pain assessments as was obviously applied to the physiological studies.

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1. O'Young J, McPeek B Quality of life variables in surgical trials. *J Chronic Dis* 1987; **40**: 513–22.
2. Clark A, Fallowfield LJ. Quality of life measurements in patients with malignant disease: a review. *J R Soc Med* 1986; **79**: 165–9.

Authors' reply

Sir

We would thank Professor Baum and Mr Roberts for their interest and their comments. We accept the criticism implied by their letter, but do not necessarily accept that their criticism could have been overcome by the methods that they suggest or, indeed, by greater effort.

Although we accept that the chart as shown in our paper is not a true linear analogue scale because numbers have been attached to the line at the time of questioning, we believe it is still a visual analogue scale. Although Scott and Huskisson[1] differentiated between verbal analogue and verbal graphic rating scales, even numerical rating scales, numerical forms of the visual analogue scale are clearly accepted by Downie *et al.*[2] and by Reading[3] to be forms of a visual analogue scale. Although Scott and Huskisson[1] showed an increase in sensitivity obtained by the linear analogue scale compared with that from a simple four point verbal rating scale, the linear analogue scale suffers from the disadvantage that many elderly or drug affected patients find difficulty in comprehending the relevance of the scheme, and improved compliance has been shown using the light analogue pain scorer in which the pain was 'rated' into five colours described by Nayman[4] or by the slide type variable resistor electronic visual analogue scorer described by Welchew[5].

Reliability is a problem with the linear analogue scale. The greater the complexity of the task and the greater its sensitivity, the less reliable it becomes[3]. Thus a linear analogue scale with an infinite number of points has greater sensitivity but lower reducibility than a linear analogue numerical graphic rating scale.

Even the linear analogue scale is subject to rating or categorizing by both the patient and the observer. It is well known that young children and deniers congregate the marks at the lower end of the scale. Those who are anxious or fearful congregate their marks at the upper end of the scale, and those who are indecisive, confused or sedated congregate theirs in the middle of the scale. Since pain scores should never be treated as parametric data, the scores themselves should be ranked or grouped for analysis, thereby introducing a rating of the patient's scoring.

We do not even accept the criticism that "comparison with other studies using 'visual analogue scores' is consequently not possible", because correlation between scales has been studied and Woodforde and Mersky[6] and Reading[3] found high correlations. Downie *et al.*[2] compared four scales including a verbal rating scale and numerical, horizontal and vertical forms of the visual analogue scale and showed relatively high correlations (all over 0·6).

Increased reliability has been given to the scale in our paper by the presentation of two fixed points. In the linear analogue scale only one point is known—that of no pain. The other, that of greatest pain imaginable, depends upon the imagination, and is altered by the patient's present experience. In our pain chart from the second postoperative day onwards there are two fixed points, that of no pain, and that of the pain of the previous day. The study of Revill *et al.*[7] suggests that the memory for the position of any previous mark on a visual analogue score is so good that it would not make much difference to the new score if the previous score was seen[8].

We have obviously considered other methods of measuring pain: consumption of analgesics, frequency of demand, cross modality matching, experimental intensity matching, McGill questionnaire, evoked responses, electro-encephalography frequency latencies, but came to the conclusion that either they were too complex to be administered in the normal clinical setting without affecting the patient's perception or anxiety, or that they were too invasive, or that they were so complex as to be unreliable. The wide range of pain scores would suggest that the method was sufficiently sensitive and that the discrimination between the two methods would not have been improved by increased sensitivity of the method of measurement of pain.

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1. Scott J, Huskisson EC. Graphic representation of pain. *Pain* 1976; **2**: 175–84.
2. Downie WW, Leatham PA, Rhind WM, Wright V, Branco JA, Anderson JA. Studies with a pain rating scale. *Ann Rheum Dis* 1978; **37**: 378–81.
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8. Dodson M. In: *The Management of Postoperative Pain*. London: Edward Arnold, 1985.

Surgical technique

Sir

Few would argue with the sentiments expressed by Mr Matheson's letter (*Br J Surg* 1987; **74**: 1190) that 'craftsmanship' in surgery is important and technical prowess a requisite for appointment as a consultant surgeon. The general acceptance of this view is the main reason why clinical ability is seldom 'aired as an important criterion of (consultant) appointments'. By the time a surgical trainee is considered for elevation to consultant status he has generally spent some 14 years in postgraduate surgical training and his 'craftsmanship' has sufficiently matured for appointment committees to be confident about technical competence—especially when supported by three testimonials from senior surgeons.

The thrust of Mr Matheson's argument, however, is not so much related to the positive acquisition of technical expertise but rather that academic and research endeavour in some mysterious way inhibits the craft of surgery. In a leading article in the same issue (*Br J Surg* 1987; **74**: 1073–4) I attempted to express the view that these two arms of surgical practice, surgical science and clinical expertise, should be intermingled in surgical training programmes.

Over the last 20 years there has been increasing acceptance that surgical training demands both the acquisition of scientific knowledge and clinical judgement, as well as technical ability. If a trainee has not been exposed to ongoing research or clinical investigation at some stage during his training he may well not be in the position to take full advantage of developments which will inevitably occur during his consultant years.

Many, if not most, consultant surgeons will admit that their own research experience has resulted in the adoption of a more critical attitude to clinical problems. This can only improve the standard of clinical care for the individual patient and the current demands for surgical audit and the assessment of cost effectiveness of operative procedures are but an example of this attitude. The present generation of practising surgeons trained, in part, in critical assessment of all that they do has resulted in overall better surgical care. Whilst technical expertise in surgical practice is absolutely essential, exposure to research endeavour amalgamated with clinical practice should not be denigrated in the overall training programme.

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Loop mattress suture

Sir

The suture technique described by Mr Gault and colleagues (*Br J Surg* 1987; **74**: 820) has been published previously[1]. The originator was a Seattle surgeon, Van Hillman, who taught the stitch to my mentor, Henry Harkins, who taught it to me. These acknowledgements were, to my embarrassment, deleted from my paper by the editor of *Surgery, Gynecology and Obstetrics*, and I am pleased to have this opportunity to set the record straight.

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1. Condon RE. Locked vertical mattress stitch for skin closure. *Surg Gynecol Obstet* 1968; **127**: 839.

Book reviews

Vascular Diseases. Current research and clinical applications

E. E. Strandness. 230 × 150 mm Pp. 491 + xv. Illustrated. 1987. New York: Grune and Stratton. $49 50.

Many of us with research experience have been honoured (flattered?) by requests to join working parties, workshops, seminars, brain storming sessions, consensus meetings etc., all of which have in common the laudable aim of getting experts together with a view to producing an almost instant 'state of the art' publication. With such a collection of talent (the argument goes), through analysis and debate new ideas will be generated and problems solved. Clearly this often happens and even the most menial workshops produce some results. Now I would argue that these results and the discussion itself should interest the outsider as much as the analysis presented in the contributor's manuscripts.

Vascular Diseases. Current Research and Clinical Applications typifies the problems which beset this kind of publication. Ostensibly the workshop was held 'with the hope that by bringing together leaders in research in this field, a definition of the present state of our knowledge and of some promising directions for future research could be made' From the workshop 'it was hoped that initiatives would be generated which might lead to the setting aside of funds for research in this area.' With such clearly defined aims, one would have thought that at least the 'definition of the present state of our knowledge' and 'directions for future research' would be identifiable; unfortunately this is not always the case. Certain chapters, for example those by Strandness and Stanley *et al.*, do address the problem, referring to 'accomplishments' and 'knowledge gaps'. Other chapters are less enlightening.

With such a wealth of talent present, it seems very sad that no attempt was made to record for posterity any of the discussions, and even sadder that the publishers failed to invest a few extra dollars in retyping one or two of the manuscripts. The one on 'angioscopy, for example, in my copy was indecipherable. Clearly the workshop was worthwhile to the participants and I enjoyed reading many of the contributions enormously, but as an exercise in communications I think the book is a failure. It is for the reader to decide how to portion the blame.

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Practical Non-invasive Vascular Diagnosis. Second Edition.

R F. Kempczinski. 158 × 232 mm. Pp. 517. Illustrated. 1987. London Wolfe Medical Publications Ltd. £43.00.

Since the first edition in 1979 of this useful guide to non-invasive vascular diagnosis there has been a dramatic increase in both new techniques and the number of clinical laboratories. This is reflected in the number and diversity of the chapters. Each chapter is a brief summary of the current state of the art of that particular subject. The opening section concerns the organization, staffing and computing of a new vascular laboratory, and is compulsory reading for anyone in that position. Other sections include the assessment of peripheral vascular disease, cerebrovascular disease and venous problems, and are both comprehensive and well written. The diagrams are uniformly simple and clear with many photographs to illustrate the clear text.

In such a rapidly expanding subject it is inevitable that there will be some newer techniques not included but overall this book is an excellent reference book for non-invasive diagnosis and can find a place in the library of any vascular surgeon with access to a vascular laboratory.

M. Horrocks

Consultant Surgeon
Bristol Royal Infirmary
Bristol
UK

Comprehensive Management of Head and Neck Tumours

Volume 1: S. E. Thawley 206 × 270 mm. Pp 1038. Illustrated. 1987. Philadelphia W. B. Saunders. £75.00.

Volume 2 S. E. Thawley. 206 × 270 mm. Pp 1916 Illustrated. 1987 Philadelphia. W. B. Saunders. £75 00.

Even within North America, head and neck oncology is not yet firmly established as a separate entity. Several different specialties are concerned with diagnosis and management of the wide variety of tumours which affect this complex area of the body. Consequently, no individual could hope to acquire enough expertise, or indeed find the time, to produce a personal up-to-date account of all facets of this ever expanding sphere of oncology. It is to the credit of the authors of these two volumes, which total some 2000 pages, that they have so successfully co-ordinated the contributions of 140 individualists to produce what is the most comprehensive and authoritative account of this subject yet available.

A total of 13 areas are covered within 26 chapters which also include important topics such as 'head and neck surgery in the aged patient' and 'statistics of head and neck tumours' Nothing important is omitted and, by using a standard format to each subject area, the opinions of many separate disciplines are collated in a logical manner.

Incidence, aetiology, clinical history and physical findings, diagnostic tests, pathology, medical and surgical treatment, rehabilitation and, finally, controversies regarding treatment regimes, make up this standard plan. Each is written by individuals whose reputation in their topic is well established. All, with a solitary exception, come from North America, however, excellent editing has largely avoided the potential problems of overlap and varying skills in expression.

Presentation of both facts and figures is good and the whole package is highly professionally produced. Because of the comprehensive and far reaching coverage of the subject, any oncologist working within the head and neck will find value in these two volumes. They are not likely to be bettered within the next decade!

D. F. N. Harrison

Professor of Laryngology and Otology
Institute of Laryngology and Otology
University of London
London
UK

1987 Yearbook of Vascular Surgery

J. Bergan and J S. T. Yao. 158 × 234 mm. Pp. 359. Illustrated 1987. London Wolfe Medical Publications. £37.00.

A synopsis of 350 selected papers on vascular surgery published between May 1985 and June 1986 is presented. I do not know why the publishers cannot restrict the papers reviewed to those published in one calendar year which would then be referred to in the title. The series is essential for the major libraries as it provides a valuable source of reference. I must say that when I sat down to read the book, I feared that it would be as boring as trying to read the BJS from cover to cover. However, I found many interesting and novel ideas and would imagine that other vascular surgeons would enjoy reading it.

J. Mosley

Consultant General and Vascular Surgeon
Leigh Infirmary
Leigh
Lancashire
UK

Erratum

Book reviews; *Current Therapy in Vascular Surgery*, reviewed by A. A. B. Barros D'Sa, *Br J Surg* 1987; 74· 1070, paragraph 1, line 13. for 'the lack of a reference list *does not* diminish the standing of the volume', read 'the lack of a reference list *does* diminish the standing of the volume'. We apologize for this error.

Notices and announcements

13–15 April 1988
Association of Surgeons of Great Britain and Ireland Annual Meeting
Harrogate, UK
Information: Barry Jackson, Hon Secretary, Association of Surgeons of Great Britain and Ireland, Royal College of Surgeons of England, 35/43 Lincoln's Inn Fields, London WC2A 3PN, UK

18–19 April 1988
Oxygen-free Radicals in Health and Disease
London, UK
Information Miss Penny Robinson, IBC Technical Services Ltd, Bath House, 56 Holborn Viaduct, London EC1A 2EX, UK

21–23 April 1988
2nd Symposium for Surgery on the Fetus
Gmunden, Germany
Information Dr Wolfgang Metka, A-4020 Linz, Hauptplatz 29, Germany

28–30 April 1988
20th Congress of the European Association for Gastroenterology and Endoscopy (EAGE)
Sirmione, Italy
Information: Professor Dr med. J. M. Kimmig, Vaihinger Strasse 43, D-7000 Stuttgart 80, FRG

5–7 May 1988
Biennial Congress of the European Council of Coloproctology 1988
Geneva, Switzerland
Information General Secretary of the European Council of Coloproctology, Policlinique de Chirurgie, Hôpital Cantonal Universitaire de Genève, 1211 Geneva 4, Switzerland

12–14 May 1988
Second Vienna Shock Forum
Vienna, Austria
Information. AUSTROPA Kongbressbüro, Friedrichstrasse 7, A-1010 Vienna, Austria

20 May 1988
British Association of Endocrine Surgeons
Cardiff, UK
Information. Mr A.W. Goode, Honorary Secretary to the British Association of Endocrine Surgeons, Surgical Unit, The London Hospital, Whitechapel, London E1 1BB, UK

23–28 May 1988
Advanced Hepato-Pancreato-Biliary Surgery
Lund, Sweden
Information: Professor Stig Bengmark, Box 5003, S-220 05, Lund 5, Sweden

25–28 May 1988
79th Annual Meeting of the American Association for Cancer Research
New Orleans, Louisiana, USA
Information Margaret Foti, Executive Director, American Association for Cancer Research, Temple University School of Medicine, West Building Room 301, Philadelphia, PA 19140, USA

29 May–3 June 1988
Second World Congress on Hepato-Pancreato-Biliary Surgery
Amsterdam, The Netherlands
Information Q. A. Laman Trip, Organizer, Alton House, Keizersgracht 792, 1017 EC Amsterdam, The Netherlands

31 May–1 June 1988
Cancer Horizons
London, UK
Information· Marie Curie Memorial Foundation, c/o European Study Conferences Ltd, Douglas House, Queen's Square, Corby, Northamptonshire NN17 1PL, UK

8–11 June 1988
The Endocrine Society 70th Annual Meeting
New Orleans, Louisiana, USA
Information: Dr D Lynn Loriaux, The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20814, USA

10–11 June 1988
3rd Steglitz Pediatric Surgical Symposium
Berlin, FRG
Information· Professor Dr J. Waldschmidt, Department of Pediatric Surgery, University Klinikum Steglitz de FU, Hindenburgdamm 30, 1000 Berlin 45, FRG

20–22 June 1988
7th International Workshop for the Study of Vascular Anomalies
Hamburg, Germany
Information· Professor Dr D. A. Loose MD, Jürgensallee 44, Hamburg 52, FRG

29 June–1 July 1988
International Symposium on Therapeutic Progress in Urological Cancers
Paris, France
Information: Dr Saad Khoury, clinique Urologique (Pr Chatelain), Hôpital de la Pitié-83, Boulevard de l'Hôpital, 75634 Paris Cedex 13, France

3–9 July 1988
16th World Congress of the International College of Surgeons
Milan, Italy
Information: Secretariat, Clinica Chirurgica III—Universitá degli Studi, Via F Sforza 35, 20122 Milan, Italy

6–8 July 1988
Tripartite Meeting: Joint Meeting of the Surgical Research Society, the European Society for Surgical Research and the Society of University Surgeons
Bristol, UK
Information: Mr D.J. Leaper, Southmead Hospital, Bristol, UK

10–14 July 1988
XII Biennial Congress of the International Society of University Colon and Rectal Surgeons
Glasgow, Scotland, UK
Information. Dr H.S. Crum, Programme Chairman, Wick, Caithness, UK

14–16 July 1988
XIIIth International Update on Liver Disease
Royal Free Hospital, London, UK
Information. Professor N. McIntyre, Academic Department of Medicine, Royal Free Hospital, Pond Street, London NW3 2QG, UK

14–19 August 1988
XII International Congress of the Transplantation Society
Sydney, Australia
Information. Congress Secretariat, 145 Macquarie Street, Sydney, NSW 2000, Australia

28 August–1 September 1988
Fifth World Conference on Lung Cancer
Interlaken, Switzerland
Information. Fifth World Conference on Lung Cancer, c/o AKM Congress Service, PO Box 6, CH-4005 Basel, Switzerland

30 August–2 September 1988
10th World Congress Collegium Internationale Chirurgiae Digestive
Copenhagen, Denmark
Information· Secretariat, Spadille Congress Service, Sommervej 3, DK-3100 Hornbaek, Denmark

8–10 September 1988
Annual Meeting of the Association of Surgeons in Training
Belfast, UK
Information: Mr Bernard Lee, Department of Surgery, Belfast City Hospital Tower, Lisburn Road, Belfast BT9 7AB, UK

3–5 November 1988
Workshop: Progress in Regional Cancer Therapy
Vienna, FRG
Information. c/o B. Schick, Adteilung fur Experimentelle, Chirurgie der I Chirurgischen Universitatsklinik, A-1090 Vienna, Alser Strasse 4, FRG

6–11 November 1988
International Congress of Paediatric Surgery
Melbourne, Australia
Information· Mr Hock L. Tan FRCS, Paediatric Surgeon, Department of General Surgery, Royal Children's Hospital, Melbourne, Victoria 3052, Australia

BOOKS FROM BUTTERWORTHS

ATLAS OF GENERAL SURGERY • Second Edition

Hugh Dudley ChM, FRCS(Ed), FRACS, FRCS
Professor of Surgery, St Mary's Hospital, London, UK

David C Carter MD, FRCS(Ed), FRCS (Glas) St Mungo Professor of Surgery, University of Glasgow; Honorary Consultant Surgeon, Royal Infirmary, Glasgow, UK

R C G Russell MS, FRCS Consultant Surgeon, Middlesex Hospital, St John's Hospital for Diseases of the Skin, and Royal National Nose, Throat and Ear Hospital, London, UK

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Virtually all the material has been previously published in the fourth edition of the authoritative Operative Surgery Series, but for this new edition of the Atlas, chapters on intestinal stapling have been included. The selection of topics has been carefully re-assessed with the needs of the general surgeon in mind, and there is now much greater emphasis on abdominal and vascular procedures.

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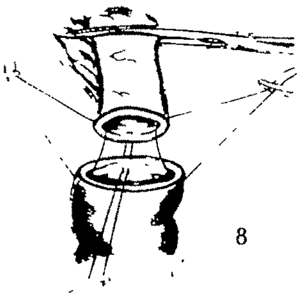
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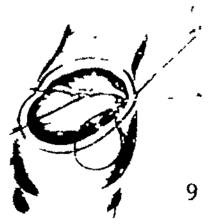
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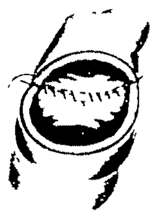
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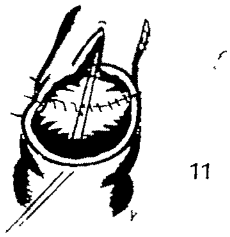
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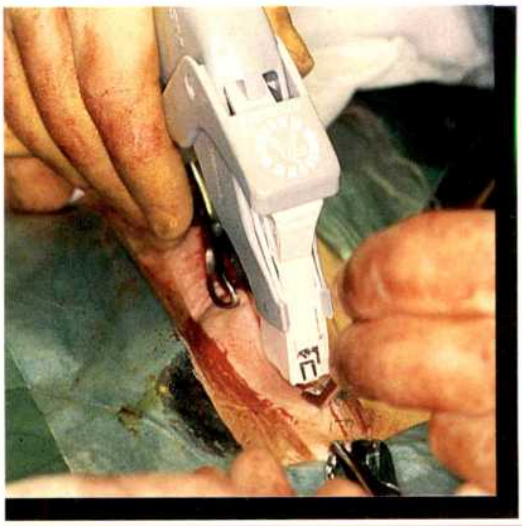

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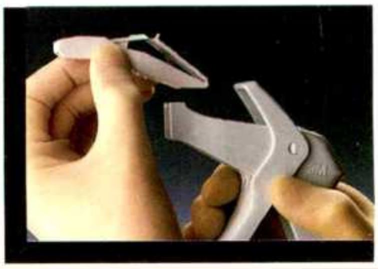

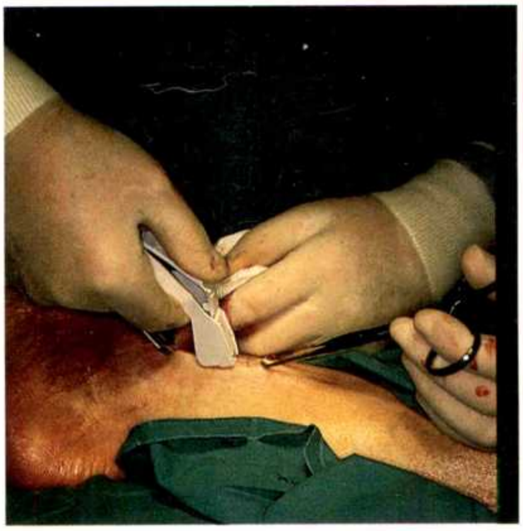

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3 Traub, A.C. and Quattlebaum, F.W. (1981) Cutaneous Wound Closure: Early Staple Removal and Replacement by Skin Tapes. Contemporary Surgery, **Vol 18.**
4 Jewell, M.L., Sato, R. and Rahija, R. (1983) A Comparison of Wound Healing in Wounds Closed with Staples Versus Skin Suture. Contemporary Surgery, **Vol 22,** 29-32.
2 Bucknall, T.E. and Ellis, H. (1982) Skin Closure. Comparison of Nylon, Polyglycolic Acid and Staples. Euro. Surg. Res., **14,** 96-97.
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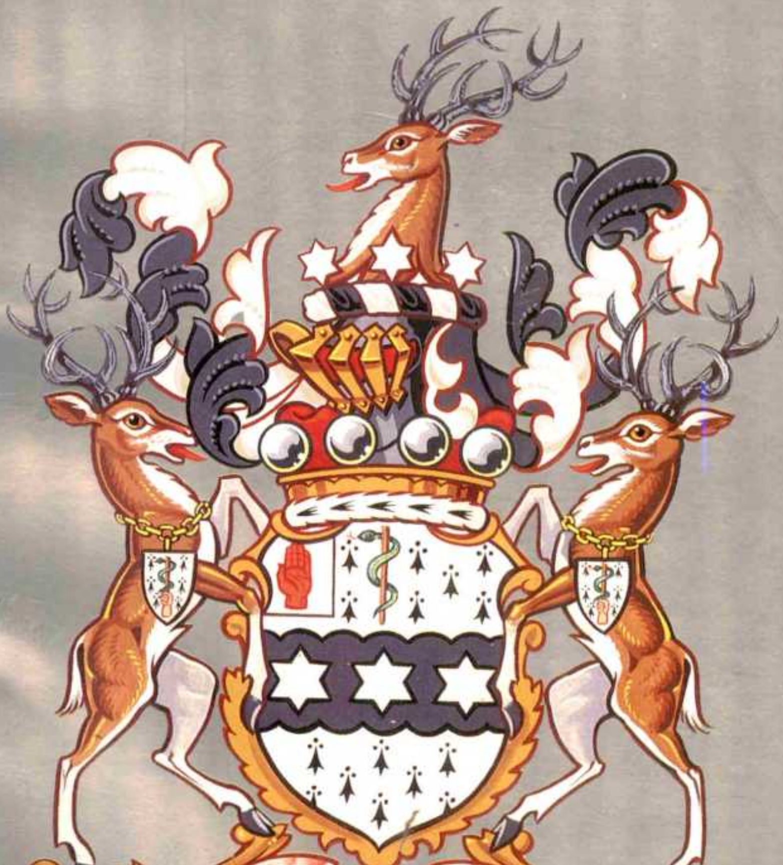

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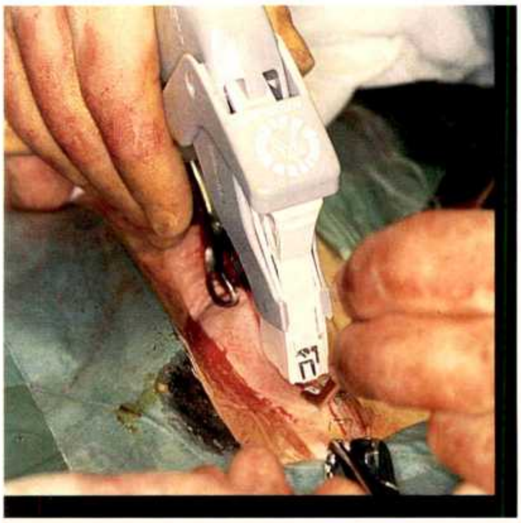

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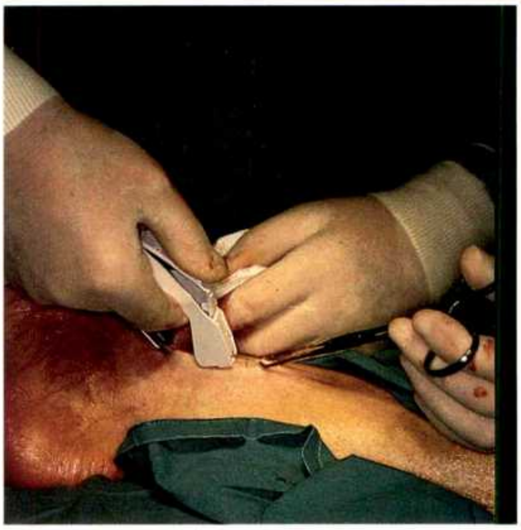

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Volume 75 Number 4 April 1988

LEADING ARTICLE

Modern treatment of varicose veins **297**
B. Eklof

REVIEW

Regional anaesthesia and surgical morbidity **299**
N. B. Scott and H. Kehlet

Management of pleomorphic adenoma of the parotid **305**
J. D. Maynard

Value of the tympanomastoid fissure in the exposure of the facial nerve (surgical workshop) **309**
H. H. Lawson

Intraparotid anatomy of the facial nerve and retromandibular vein **310**
M. R. Laing and W. S. McKerrow

Incidence and diagnosis of parotid gland tuberculosis in Asians in Leicester **313**
S. S. Ubhi, J. P. Neoptolemos and D. F. L. Watkin

Risk to surgeons: survey of accidental injuries during operations **314**
S. A. Hussain, A. B. A. Latif and A. A. A. A. Choudhary

Surgical glove perforations **317**
S. J. Brough, T. M. Hunt and W. W. Barrie

Comparison of colonic reservoir and straight colo-anal reconstruction after rectal excision **318**
R. J. Nicholls, D. Z. Lubowski and D. R. Donaldson

Clinical and functional results after restorative proctocolectomy **321**
M. Pescatori, C. Mattana and M. Castagneto

Influence of proximal colostomy on the healing of a left colon anastomosis: an experimental study in the rat **325**
P. Udén, P. Blomquist, H. Jiborn and B. Zederfeldt

Role of collagenase in colonic anastomoses: a reappraisal **330**
N. L. Chowcat, F. J. Savage, R. M. Hembry and P. B. Boulos

Resectability rate of hepatocellular carcinoma in rural southern Africans **335**
Rinah Maraj, M. C. Kew and R. J. Hyslop

Parastomal hernia in relation to site of the abdominal stoma **339**
R. Sjodahl, B. Anderberg and T. Bolin

Fulminant pseudomembranous colitis with left hemicolon and rectal sparing (case report) **341**
J. A. Cumming, B. G. McCann and D. N. L. Ralphs

Growth-promoting action of gastrin on human colonic and gastric tumour cells cultured *in vitro* **342**
S. A. Watson, L. G. Durrant and D. L. Morris

REVIEW

Bacterial short-chain fatty acids and mucosal diseases of the colon **346**
W. E. W. Roediger

The pulsed dye laser and atherosclerotic vascular disease **349**
A. Murray, P. R. Crocker and R. F. M. Wood

Venous reflux: quantification and correlation with the clinical severity of chronic venous disease **352**
D. Christopoulos, A. N. Nicolaides and G. Szendro

Evaluation of peritoneal tube grafts in the inferior vena cava of the pig **357**
Else B. Ribbe, P. Alm, E. Hallberg and L. E. H. Norgren

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Erosion of rectum by Tenckhoff catheter (case report) 360
M. H. Jamison, S. J. Fleming, P. Ackrill and P. F. Schofield

Pulse-generated runoff: a new method of determining calf vessel patency 361
J. D. Beard, D. J. A. Scott, J. M. Evans, R. Skidmore and M. Horrocks

Dihydroergotamine and the thromboprophylactic effect of dextran 70 in emergency hip surgery 364
M. Rorbæk-Madsen, B. W. Jakobsen, J. Pedersen and B. Sørensen

Changes in plasma and buffy layer vitamin C following surgery 366
S. Vallance

Surgical care of patients over eighty: a predictable crisis at hand 371
J. H. Williams and J. Collin

Incisional hernia in re-opened abdominal incisions: an overlooked risk factor 374
P. M. Lamont and H. Ellis

Consequences of blood loss on growth of artificial metastases 377
S. K. Singh, R. L. Marquet, R. W. F. de Bruin, W. C. J. Hop, D. L. Westbroek and J. Jeekel

Fine needle aspiration cytology: an *in vitro* study of cell yield 380
M. N. Hartley, D. J. Tuffnell, Jane L. Hutton, Margaret Palmer and M. S. Al-Jafari

Operative treatment of median cervical cysts 382
G. W. M. Tetteroo, J. P. Snellen, P. Knegt and J. Jeekel

Carcinoma of the ileostomy in a patient with familial adenomatous polyopsis (case report) 384
J. N. Primrose, P. Quirke and D. Johnston

Abnormal connecting duct between the common bile duct and the pancreatic duct (case report) 385
A. R. Rosseland, L. P. Eltvik, B. Gundersen and A. Bakka

Traumatic disruption of the gallbladder evaluated by computerized tomography and magnetic resonance imaging (case report) 386
F. J. Blaumgartner, M. J. Barnett, M. Velez and L. C. Chiu

VASCULAR SOCIETY ABSTRACTS 388

CORRESPONDENCE 396

ERRATUM 398

BOOK REVIEWS 399

NOTICES AND ANNOUNCEMENTS 400

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Lord Lister Coat of Arms

The original painting of the Arms shown on the cover of the Journal was prepared under the direction of York Herald of Arms (Conrad Swan CVO, PhD, FSA).

The first issue of The British Journal of Surgery

The first number of *The British Journal of Surgery* duly appeared in July 1913, under the direction of an editorial committee chaired by Moynihan with Hey Groves as the Editorial Secretary. This type of direction, by committee with an editorial secretary rather than by an editor with executive function, continued until 1979.

In the first issue an introductory by Sir Rickman J. Godlee, Baronet, KCVO, President of the Royal College of Surgeons of England, set the scene: 'Some apology is perhaps called for in these days, when the surfeit of medical literature placed before the enquiring student almost destroys his appetite by its very abundance'. The neonate *British Journal of Surgery* should be 'worthy of a place amongst the Centralblatts, Archives and Annals with which we are familiar... a medium through which we can make our voice intelligibly heard'.

This issue contained ten original papers, a biography of Lister, 'instructive mistakes', 'rare cases', 'notices of books' and 'visits to clinics' (Professor Sir William MacEwen at Glasgow and Professor Tuffier in Paris). The papers were more widely distributed over surgical topics than today, including: anaesthesia, shock, orthopaedic, urology, thoracic, faciomaxillary and hepatobiliary surgery. All the papers were carefully referenced though, alas, the references do not conform to current BJS requirements!

For general surgeons, D'Arcy Power's paper on gallstones is perhaps the most revealing and time locked. D'Arcy Power reviews 90 patients treated by himself; there were no deaths in 26 uncomplicated cases, but with minor complications the operative mortality rose to 22 per cent and with major complications to 55 per cent 'but this should be looked upon as 45 per cent saved'. Jaundice led to a particularly unfavourable outcome. Making a plea for earlier surgery for gallstones D'Arcy Power continues, 'When an operation is decided upon for the removal of gallstones at the present time it is usually done at an earlier period in hospitals than in private practice. The wealthier class nearly always postpone a visit to the surgeon.... The more difficult cases, and those attended by the highest mortality, are more likely to occur in private than in hospital practice. There ought to be no such difference. Poor and rich should alike receive the same advice.'

Over the early years the Editorial Committee had to grapple with all the problems the Editorial Committee still face today. An early problem was the substandard submission. Moynihan and Hey Groves were quite adamant that the submitted paper was to be reviewed by two committee members, a decision reached, then, as the minute book obliquely puts it, 'sent back'. Early casualties of this peer review include Milligan, Irvin, Pybus and Jefferson; Maxwell's article on Paget's disease of the nipple was declined on the grounds 'that the expense of reproduction of the coloured illustrations was out of proportion to the value of the article'. Dr Matas' paper on aneurysm was not accepted because 'it had already appeared'. Indeed, 1 year later in 1915 a signed declaration from the author was introduced in an attempt to curb this malpractice Notwithstanding, in 1916 Sir W. Cheyne simultaneously published the same article in the *British Medical Journal*, the *Lancet* and *The British Journal of Surgery*! No matter how important the author, or even if they were a member of the committee, the rules still applied. 'Mr D'Arcy Power's Bradshaw lecture was accepted provided it had not appeared elsewhere, either as a whole or in abstract before publication in *The Brisith Journal of Surgery*'. The problem of double publication still plagues us. Also, 'It was decided that books not of sufficient merit be given notices only'.

A policy of taking papers only from the United Kingdom and British Empire was held to at first. Eminent continental professors had papers refused: the minutes record 'to return Dr Ricardo Finochetto's paper and to state contributions from foreign sources were not received'. Then in 1917 Harvey Cushing (an old Moynihan friend) submitted an extended paper on head injuries; this jewel could not be turned down and wisely the committee changed the rules! In 1913 and 1914 German clinics were to be visited and German language journals and books were exchanged, but by August 1914 this was no longer possible. It is, however, a great credit to Hey Groves' and Moynihan's humanity that immediately after the Armistice in 1918 they resumed their German contacts; *The British Journal of Surgery* was sent to Berlin and the Zentralblatt Organ für Chirurgie was given in exchange.

The 1914–18 War gave the journal a great and unexpected opportunity The optimists thought 'the show' would be over in months and the Journal should cease publication for the duration but Moynihan and Hey Groves thought otherwise—they went off to war and kept *The British Journal of Surgery* going too! Indeed, *The British Journal of Surgery* contributed greatly to the war effort, publishing, as the official censor would allow, accounts of battlefield injuries and their management.

After the Great War *The British Journal of Surgery* was established and its circulation increased steadily; undoubtedly its contribution to the war effort was an important factor in proving its importance. From the figure of 7124 copies sold in 1913 we estimate to sell in excess of 80 000 copies in our 75th Jubilee year The range of topics included has changed over the years. In the 25 years 1938–63 experimental surgery and shock research blossomed whereas from 1963 to 1988 research into metabolism and transplantation has increasingly found space in our pages. The source of the contributions has shifted too and today we have a smaller proportion of papers (but more papers in real terms) from the British Isles. Over the last 25 years our integration into Europe has resulted in a surge of papers from our co-citizens in the Old World

H. B. Devlin

Table 1 *Topics included in* The British Journal of Surgery *over 75 years*

	1913	1938	1963	1988 (Estimated)
Total number of pages	748	1118	990	1294
Total number of papers	46	85	134	284
Visceral surgery (%)	28	21	42	30
Breast surgery (%)	—	5	5	5
Vascular surgery (%)	—	6	7	10
Urological surgery (%)	7	14	8	1
Thoracic surgery (%)	7	2	3	4
Orthopaedic surgery (%)	28	15	10	—
Plastic surgery (%)	9	1	—	—
Neurological surgery (%)	7	5	3	—
Head and neck surgery (%)	—	11	5	5
Anaesthesia (%)	4	1	—	1
Other (%)	10	19	17	44

Table 2 *Source of contributions to* The British Journal of Surgery *over 75 years (Hey Groves classification)*

Source of papers	1913	1938	1963	1988 (Estimated)
Number of papers	46	85	134	284
England and Wales (%)	88	75	73	55
Ireland (North and South) (%)	8	—	(1 paper)	10
Scotland (%)	2	9	7	10
Dominions and Colonies (%)	1	10	17	10
Europe (%)	—	—	—	15
America (excluding Canada) (%)	1	3	2	<1
Other (%)	—	3	(1 paper)	<1

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Leading article

Br. J. Surg. 1988, Vol 75, April, 297–298

Modern treatment of varicose veins

Ad utrumque paratus is the old device on the Seal of the University of Lund. Its meaning—prepared for both the sword as well as the book—can be transcribed for the modern treatment of varicose veins: use the knife as well as the syringe. Varicose veins were recognized and treated by the Ancient Egyptians and it is surprising that more than 3000 years later there is no agreement on the best mode of treatment. How opinions have varied during this century is exemplified by Karl Lofgren's[1] description of the Mayo clinic methods of treatment: 1900–1927 extraluminal stripping, 1927–1936 sclerotherapy, 1936–1947 ambulatory high ligature with sclerotherapy, 1947 until now, radical surgery supplemented by sclerotherapy.

Diagnosis of venous insufficiency

Most of us use inspection, palpation and the tap-cough-thrill test to diagnose venous insufficiency although the clinical value of this test has been questioned by the St. Thomas' group. Even the accuracy of the tourniquet test and Doppler ultrasound has been challenged in the diagnosis of long saphenous vein incompetence[2]. However, we can still reach a reliable clinical diagnosis in the majority of patients with venous insufficiency, especially if simple non-directional Doppler ultrasound is used routinely. We can evaluate obstruction, patency or reflux in the superficial as well as the deep venous system. The vascular laboratory and phlebography will only be necessary in a few cases where symptoms and clinical findings correlate poorly or indicate a deep venous problem or congenital angioplastic dysplasia. The advent of venous reconstructive surgery puts more emphasis on a correct diagnosis as there are now possibilities for improving the patient's venous function in venous obstruction and also in the case of incompetent venous valves. The Mecca for evaluation of venous function today is London with St. Mary's and St. Thomas' hospitals where non-invasive methods including the duplex Doppler have been developed. However, the Medina for venous reconstruction must be looked for in the USA.

Treatment of varicose veins

Ouvry and Davy[3] have written 'In the past there were two camps. In one, varicosities were treated entirely by surgery. In the other, entirely by sclerotherapy. The relations between the two camps were difficult and rare . . .'. Both methods improved, so that 'it was possible to associate the advantages of the two modalities, avoiding their inconveniences for the good of the patients'. Positive but wishful thinking, unless we can get the two camps together. Three prospective randomized studies with long-term follow-up, comparing surgery with compression sclerotherapy, are now available. In Sweden, Einarsson found good immediate results after either treatment but there was a rapid deterioration in the compression sclerotherapy group which was already apparent after 6 months (Einarsson E, personal communication). After 5 years, < 10 per cent of the patients in the compression sclerotherapy group were cured compared with 60 per cent in the surgical group. Assessment of venous function using foot volumetry corroborated the clinical results. Combination of compression sclerotherapy with high ligature of the long saphenous vein under local anaesthesia gave intermediate results with a good initial result but recurrence in 60 per cent of patients after 1 year and in 80 per cent after 5 years. The results of this study show the same trends as those found in the previous studies by Hobbs[4] and by Hamilton Jacobsen[5].

The consensus among most vascular surgeons today is that an abnormal long saphenous vein should be stripped. Most surgeons prefer a formal high ligature in the groin with stripping of the long saphenous vein to just below the knee avoiding the saphenous nerve and sparing the distal long saphenous vein for future bypass surgery. The heated argument about whether one should avoid stripping the long saphenous vein and only do a high ligature, so as to retain it for future bypass grafting, appears to have cooled down. In 87 per cent of one series of patients peroperative retrograde saphenography revealed at least one Hunterian perforator which could perpetuate long saphenous vein incompetence after high ligature; in 65 per cent of cases the long

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saphenous vein was found to be varicose, rendering it useless as a graft[6]. Furthermore, less than 3 per cent of 440 patients who underwent stripping at the Mayo Clinic needed bypass surgery after 20 years of follow-up[7].

The role of the short saphenous vein has been emphasized as its incompetence is often overlooked. Hobbs[8] has advocated peroperative phlebography to elucidate the wide variations in the termination: in 60 per cent of cases there is a true saphenopopliteal junction, in 30 per cent there is a high termination in the long saphenous vein or deep vein, and in 10 per cent of cases it terminates in calf veins. Compression sclerotherapy can be used as postoperative adjuvant treatment in patients with main stem insufficiency. It is also a good method in patients with incompetent perforators and can be used to palliate complications due to the post-thrombotic syndrome and congenital angioplastic dysplasias such as the Klippel–Trenaunays syndrome. Dormandy's group[9] has shown that the average bandage time should be 3 weeks, but it has to be individualized. Isolated dilated veins and cosmetically undesirable veins should be treated by compression sclerotherapy.

Socio-economic considerations

Varicose veins are very common and demand a substantial part of hospital resources. In order to decrease the costs for society without impairing the quality of care we must try to shorten hospital stay and introduce ambulatory surgery and compression sclerotherapy. In Sweden[10] 20 per cent of patients are currently operated upon as in-patients with an average stay of 3 days. The remaining 80 per cent are operated upon on an ambulatory basis under general or epidural anaesthesia. Based on the results of randomized trials we have calculated that 20 per cent of the patients could have compression sclerotherapy as an alternative to surgery. As the costs for compression sclerotherapy are calculated as amounting to 15 per cent of the total costs for in-patient surgery, this could decrease the costs to society by 30 per cent in comparison with the sole use of in-patient surgery.

Discussing varicose veins makes me think of Erich Maria Remarque's novel from World War I—'In Westen nichts Neues'. But this pessimistic view is not well founded. International awareness of the problem with an increased level of scientific activity will certainly improve the management of this common if not lethal disorder, and hopefully bring the surgical and sclerotherapy camps closer. The modern surgeon treating varicose veins should have a Doppler in his pocket with a knife in one hand and a syringe in the other—*ad utrumque paratus.*

B. Eklof

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PO Box 24923
Kuwait

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Regional anaesthesia and surgical morbidity

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This review assesses the results of studies examining the influence of regional anaesthesia on surgical morbidity. Morbidity appears to be reduced when procedures below the umbilicus are concerned, but evidence is less convincing for upper abdominal and thoracic procedures.

Keywords: Regional anaesthesia, operations, morbidity

In the past few decades considerable advances have been made towards a better understanding of the metabolic effects after surgery[1,2], coinciding with a rapid expansion in anaesthetic knowledge and technique. With these has developed the concept of 'stress-free anaesthesia'[3] and its protagonists argue that the side-effects of surgery may, in fact, not only be related to imperfections in perioperative technique, but rather result from the increased demands on the body caused by the marked catabolic response which occurs after injury/trauma[3,4]. This being the case, one may reason that techniques which modify this response and maintain organ function might lead, *per se*, to a reduced morbidity[4].

While regional anaesthesia in its present form is not ideal, it is currently the most effective method of reducing the stress response[4] and in this article the existing data from controlled clinical studies on its effects on organ function and major postoperative complications are reviewed. It should be emphasized that the use of local or regional anaesthesia does not imply operating on a conscious patient. In some of the studies, the patients receiving regional anaesthesia were also given a light general anaesthetic during surgery, and other studies suggest that the modifying effect of regional anaesthesia on the metabolic response is not altered by addition of general anaesthesia[4].

Mortality

Mortality is a crude but, nevertheless, well-defined endpoint. However its incidence in modern elective surgery is very low, necessitating large numbers of patients to be studied before any benefit can be attached to a particular regimen.

There exist, however, 12 controlled mortality studies[5–16] comparing regional anaesthesia (RA) with general anaesthesia (GA) in patients undergoing acute hip surgery. These patients are elderly, often malnourished with concomitant multisystem disease or dysfunction and thus provide a high-risk study population. Although only two of these studies showed a significant benefit from RA on short-term survival[6,9], pooling of data shows that overall there is approximately a 30 per cent reduction in early mortality in the RA group (RA = 65/941 = 6·9 per cent; GA = 107/1037 = 10·3 per cent; $P < 0{\cdot}01$). As shown in *Figure 1* the results of the different controlled trials in patients receiving spinal or epidural anaesthesia *versus* general anaesthesia show either a reduction or no change in early postoperative mortality, except in one study[16] where mortality was insignificantly higher in the spinal group (6·6 per cent *versus* 5·9 per cent). This study is the only multicentre study, but the trend towards higher mortality in the spinal group was seen in the results from four of six participating centres. The general protocol in all these mortality studies (*Figure 1*) was fairly uniform with a limited variability in surgical procedure as well as technique of regional anaesthesia. Therefore, though concerns have been expressed about the validity of combining results of clinical trials (meta-analysis)[18,35] it may be justified in this case owing to the acceptable uniformity of the reported studies. However, since most patients came from two studies[5,16] which together showed only a very marginal (and insignificant) reduction in mortality, no final conclusion can be given, although it is highly unlikely that RA was harmful to these patients. When patients were followed up for between 2 months and 2 years, however, an initial difference in mortality disappeared[5–7,10,16].

Summarizing, RA would probably appear to reduce early postoperative mortality after acute hip surgery for fracture but long-term survival of patients is, not surprisingly, dependent on factors other than the choice of anaesthetic. The large amount of data suggests that RA should be used on these patients whenever possible.

While data from other procedures are few and inconclusive, except for one study demonstrating significantly reduced mortality in high-risk patients undergoing thoracic, abdominal or vascular procedures under an epidural analgesic regimen[17], further evaluation is merited.

Pulmonary complications

Many factors affect postoperative lung function including age, smoking, sex, personality, pre-operative status, site and duration of surgery, blood loss and sleep patterns[19,20]. It is generally believed that the functional residual capacity (FRC) is the most significant lung parameter because it alters the relationship between lung closing volume and end tidal volume thereby predisposing to atelectasis[21,22]. Although no available technique manages to prevent a reduction in FRC postoperatively, epidural analgesia seems to be better than other regimens in minimizing the reduction of this and other parameters of respiratory function[20–23]. Again, however, few studies have compared the incidence of pulmonary infections with the choice of anaesthetic[7,13–15,17,23–34]. Only three[17,24,34] have shown RA to be of clear benefit after cholecystectomy[24], lower limb vascular surgery[34], or thoracic, abdominal or vascular procedures in high-risk patients[17]. Pooling of data shows that pulmonary infection was observed in only 12·8 per cent of RA patients compared with 26 per cent in the

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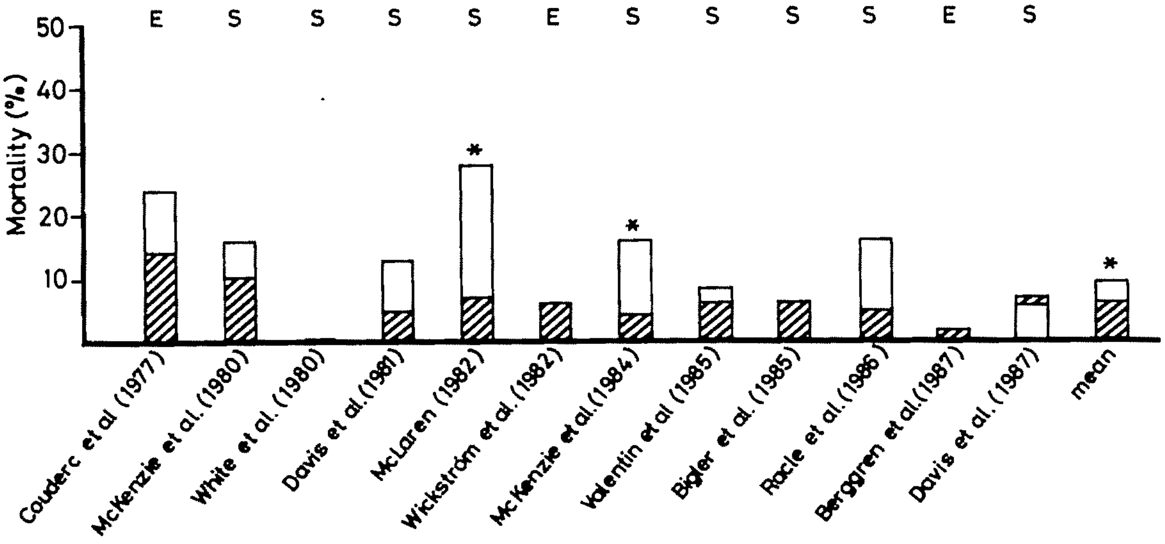

Figure 1 *The influence of regional* (■) versus *general* (☐) *anaesthesia on mortality within 30 days of acute hip surgery (cumulative data from controlled studies*[5–16]*). E, Epidural, S, spinal;* *$P<0·05$

GA group (RA = 59/460; GA = 128/492; $P < 0·0002$). In contrast to the pooled data on mortality, however, these figures are the result of a wide variety of surgical procedures as well as of different techniques of spinal and epidural analgesia. Combining results of these controlled trials therefore is not justifiable[18,35], but should encourage further properly conducted controlled trials before valid clinical recommendations can be made. The use of wound infiltration or intercostal blockade on postoperative pulmonary complications is probably of no clinical value, because the published data have shown conflicting results[36–40].

Cardiac complications

There is always concern about the development of serious hypotension and myocardial ischaemia after a high blockade under RA and concomitant GA. Nevertheless, cardiac output is well-maintained during induced hypotension under epidural anaesthesia in the absence of cardiac depressants and increased vagal activity[41], and there is also good evidence that the perioperative demands on the heart are reduced by RA[41,42] probably because of the diminished catecholamine response to surgery.

In a controlled series[42] of a very high risk group of 45 patients within 3 months of myocardial infarction undergoing urgent major vascular surgery, epidural anaesthesia conferred significantly better intra-operative stability and an insignificantly reduced re-infarction rate compared with GA (1/23 *versus* 5/22, $P > 0·2$). Postoperative death from myocardial infarction was 1/23 *versus* 3/22 patients in the RA and GA group, respectively. In a recent study comparing combined GA and epidural analgesia (bupivacaine plus opiates) *versus* GA and systemic opiates postoperatively in high risk patients undergoing thoracic, abdominal or vascular procedures the incidence of postoperative cardiovascular failure was significantly reduced by the epidural regimen[17].

Accumulated data from other studies looking specifically at perioperative electrocardiograph changes show an insignificant reduction in the incidence of ischaemic changes among the RA group (RA = 28/188 (14·9 per cent), GA = 49/242 (20·2 per cent), ($P > 0·05$)[7,10,25,30,32].

Gastrointestinal complications

Ileus

The underlying mechanism(s) of this condition still has to be clarified but sympathetic inhibitory reflexes and the local release of humoral factors appear to play important roles[43]. Epidural anaesthesia enhances gastric emptying as determined by paracetamol absorption[44], increases stomach and small bowel electrical activity[45] and, after distal colonic resection, has led to a reduction in large bowel transit time, but only if continued for 48 h[46,47], because no reduction was achieved with a 24 h infusion[48].

Intraperitoneal bupivacaine has also been shown to shorten the period of colonic inhibition following cholecystectomy[49].

Anastomoses

By increasing colonic blood flow[50], diminishing the need for neostigmine (a powerful cholinergic drug used to reverse muscle relaxants, which may increase the incidence of leaks[51]), and possibly by reducing blood loss (see below), one might expect a beneficial effect from epidural blockade on the incidence of anastomotic dehiscence. However, no prospective controlled data exist.

Three documented cases of intra-operative[52] and immediate postoperative[52,53] anastomotic dehiscence under regional anaesthesia exist, but this hardly justifies the recommendation that bowel surgery be a contra-indication to the use of RA techniques. Indeed, in these cases the increased colonic activity may have served to expedite the diagnosis of surgical imperfection at a time when the patient's condition remained optimal. Further studies are obviously needed to clarify this controversial issue.

Immunocompetence and incidence of infective complications

The development of sepsis continues to be an important factor contributing to surgical morbidity. Patients susceptibility to infection may be exacerbated by the immunosuppression which occurs after surgery and which may last for several days, or even longer in patients with malignant disease[54,55].

While local anaesthetics in pharmacological doses inhibit leucocyte metabolism and phagocytosis *in vitro* and leucocyte adherence both *in vitro* and *in vivo* by a membrane stabilizing action[56], regional anaesthetic techniques prevent some aspects of immunosuppression after hip surgery presumably by attenuating the cortisol response[56]. As immunosuppression is currently of great interest, particularly in transplant and cancer surgery and because no conclusive data exist comparing the incidence of wound infection using different anaesthetic techniques, further studies should be performed.

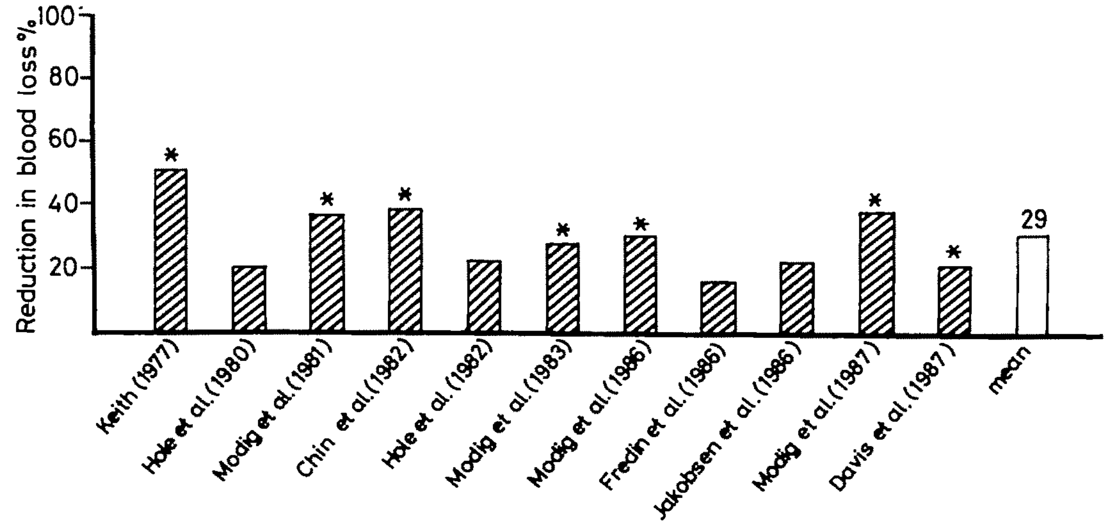

Figure 2 *The reduction in blood loss (%) achieved using regional anaesthesia* versus *general anaesthesia for elective hip surgery (controlled studies*[27,57,59–67]*).* *$P<0{\cdot}05$

Blood loss

With the growing concern regarding both the transmission of AIDS and the development of tumour recurrence after blood transfusion, any technique which can minimize perioperative blood loss is to be recommended.

The relationship between induced hypotension and blood loss is not clear, although this is the explanation commonly given for reduced losses under extradural/spinal anaesthesia and the resulting sympathetic blockade. A recent prospective controlled study on patients undergoing total hip replacement showed that under epidural anaesthesia, mean arterial pressure, mean pulmonary arterial pressure, right atrial pressure and peripheral venous pressure were all significantly reduced for the period of blockade and from this it was deduced that reduced blood loss was probably a result of diminished venous oozing[57].

With RA, intra-operative blood loss has been significantly reduced by as much as 45 per cent during hysterectomy[58], 30 per cent during lower limb vascular surgery[34], 51 per cent in lower limb amputation[28], 20–50 per cent during elective hip replacement[27,57,59–67] (*Figure 2*), 35 per cent during retropubic prostatectomy[68] and finally by 18 per cent following transurethral prostatectomy (TURP)[69], although this latter reduction did not achieve statistical significance. Another study has demonstrated a 38 per cent decrease in transfusion requirements ($P<0{\cdot}05$) in order to maintain haematocrit as opposed to replace blood loss after TURP[70]. Abdominal procedures under thoracic or lumbar epidural anaesthesia have failed to show any significant reduction, although the amount of transfused blood was lower[26,71–75].

Thrombo-embolism

Coagulation and fibrinolysis are profoundly altered after surgery, the ability to coagulate increasing while fibrinolysis, after initial enhancement, is subsequently decreased. These changes appear to be only slightly dependent on neurogenic or adrenal stimuli[56,66]. Despite this, RA may have a beneficial effect on all three components of Virchow's triad[76], as a result of reduced platelet aggregation[70,77] and blood viscosity[78], preservation of endothelial structure and a greatly enhanced lower limb blood flow[56,79].

Again, we see a highly significant reduction in the incidence of thrombo-embolism for operations below the umbilicus (*Figure 3*)[8,62–64,68,80]. Similarly, the incidence of pulmonary embolism as assessed by perfusion lung scanning was significantly lower in patients receiving RA as opposed to GA[63,64]. All the quoted studies by Modig *et al.*[63,64] are independent of one another.

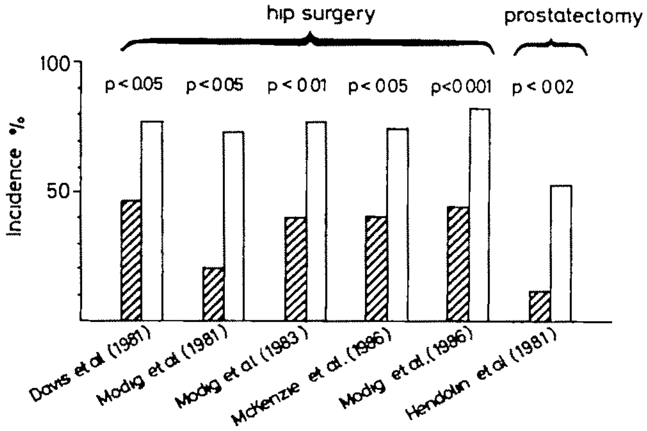

Figure 3 *The influence of regional* (▨) versus *general anaesthesia* (☐) *on the incidence (%) of postoperative deep venous thrombosis following hip surgery*[8,62–64,80] *and prostatectomy*[68] *(controlled studies)*

Although, in three studies[26,71,72] on upper abdominal surgery no difference was found in two studies[71,72], these patients were given thoracic as opposed to lumbar epidural blockade. Sympathetic blockade and thereby increased flow to the lower limbs will only occur if the block involves the L_1 and L_2 spinal nerves. The third study[26] is unique in that DVT prophylaxis was given to the control group but not to the epidural lumbar group, and showed that lumbar epidural anaesthesia alone was as effective as subcutaneous heparin. As yet, no study has been performed combining RA with other forms of DVT prophlaxis, except one hip replacement study where additional epidural analgesia did not further reduce the incidence of leg thrombo-embolism or positive pulmonary scintigrams in patients receiving antithrombotic treatment[67] with dextran 70.

Cerebral function

Despite the commonly held belief that mental performance is less affected by RA, the available data on this subject are conflicting[7,14,15,27,28,34,81,82]. Furthermore the mechanism which leads to the transient mental deterioration which occurs, has not been elucidated. It would appear, however, that the choice of anaesthesia and the altered endocrine milieu do not initiate these mental changes[15,82]. In addition a recent study has highlighted the importance of the pre-operative use of anticholinergic drugs and a history of depression in precipitating confusion[15].

Convalescence and hospital stay

No comparative data exist for such considerations on postoperative fatigue, muscle performance and return to work. The time for ambulation after hip surgery was reduced in two of three studies[5,14,30].

In a study comparing local infiltration of lignocaine with general surgery for short-stay inguinal hernia[83] the RA group could ambulate, eat and pass urine significantly earlier ($P<0{\cdot}05$) but the discharge rate at 24 h was similar for the two groups. Another study[84] comparing a low-dose continuous combined morphine and bupivacaine regimen with both systemic opiates and three other epidural regimens after abdominal surgery showed that this combined regimen provided superior pain relief and significantly improved ambulation postoperatively.

Postoperative mobilization and length of hospital stay has also been reduced by RA in eight of ten studies[5,7,17,25,29,30,32,36,38,69], but has only achieved statistical significance in one[30]. It should be further emphasized that these studies combine a variety of surgical procedures and anaesthetic techniques and thus no conclusion may be drawn. However, the accumulated mean reduction in hospital stay of 1·5 days (about 15 per cent of the total hospital stay) requires further studies to be performed.

Discussion

In this article we have reviewed existing data from controlled trials on various morbidity parameters after surgery, that have compared regional with general anaesthesia. There would certainly appear to be a reduced morbidity under RA for operative procedures below the umbilicus, contrary to other views[85] and, possibly, because the stress response can be attenuated and organ function is favourably influenced. The argument is less convincing for surgery in the upper abdomen and thorax, where coincidentally it is not possible to prevent the stress response[3,4]. However, since single studies rarely have been conclusive, results of different trials have been combined in order to achieve potentially useful information. But again we would emphasize that the criteria to perform such a meta-analysis[18,35] have not been fulfilled in all morbidity parameters considered, with the exception of blood loss and mortality after hip surgery.

Although complications have been reported after the insertion of epidural catheters, these are rare when the catheter is managed by an experienced anaesthetist. For analgesic purposes alone, RA is safe and effective and possibly a better alternative to traditional systemic analgesics provided the medical and nursing personnel are familiar with its problems[84,86]. However, we wish to stress that epidural and spinal techniques are potentially dangerous in the hands of inexperienced personnel but feel that a discussion of these problems is beyond the scope of this review. Furthermore, the published data, which will contain morbidity due to risks of RA, do not lend support to this suspicion.

Recent mortality studies have pointed the way towards a more combined approach between anaesthetists and surgeons to prevent postoperative complications and the studies of Hendolin[25], Hjortsø *et al.*[26] and Yeager *et al.*[17] have in addition provided a foundation for investigating morbidity. We hope that this article has reinforced the need for a combined approach between surgeons and anaesthetists and that it will encourage further much needed investigations into a highly important clinical area. Future studies should focus in particular on specific operative procedures and well-defined patient groups. With regard to the technique of RA, there is still some question whether a single dose or a continuous infusion is best, but metabolic data suggest a more pronounced effect with the continuous infusion[4,5].

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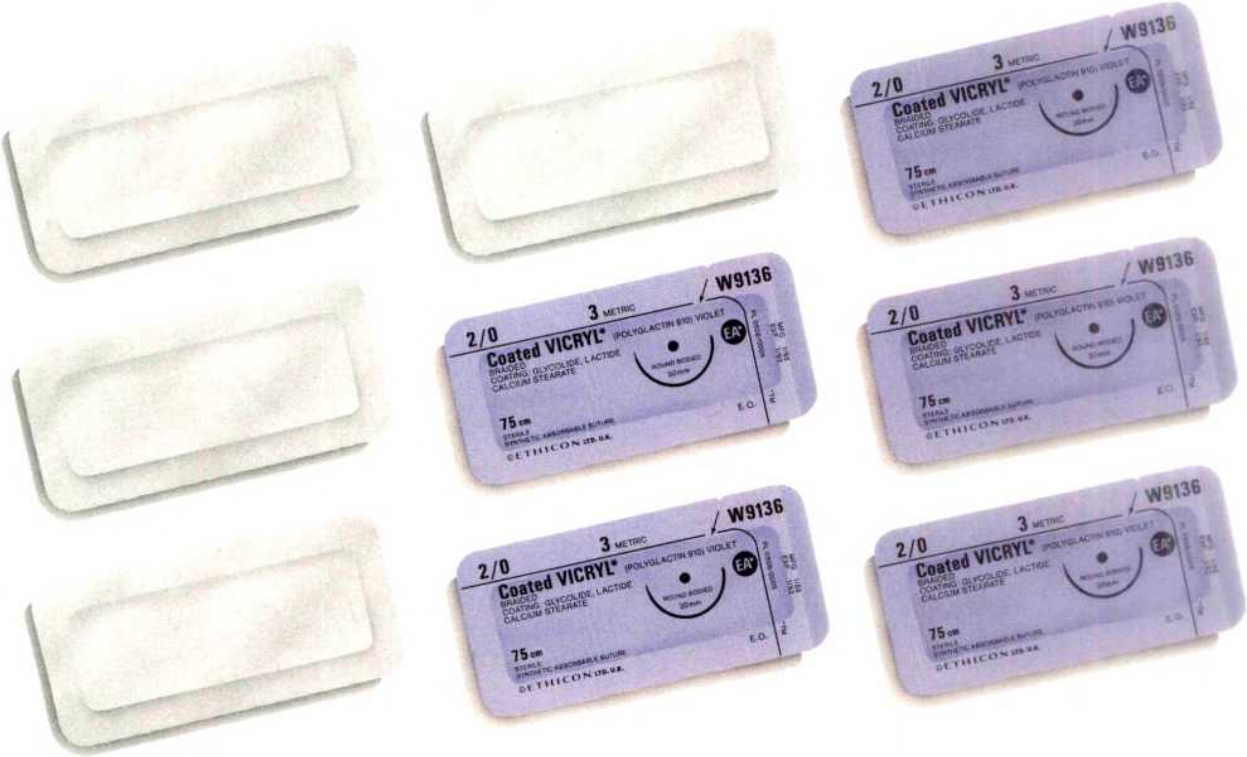

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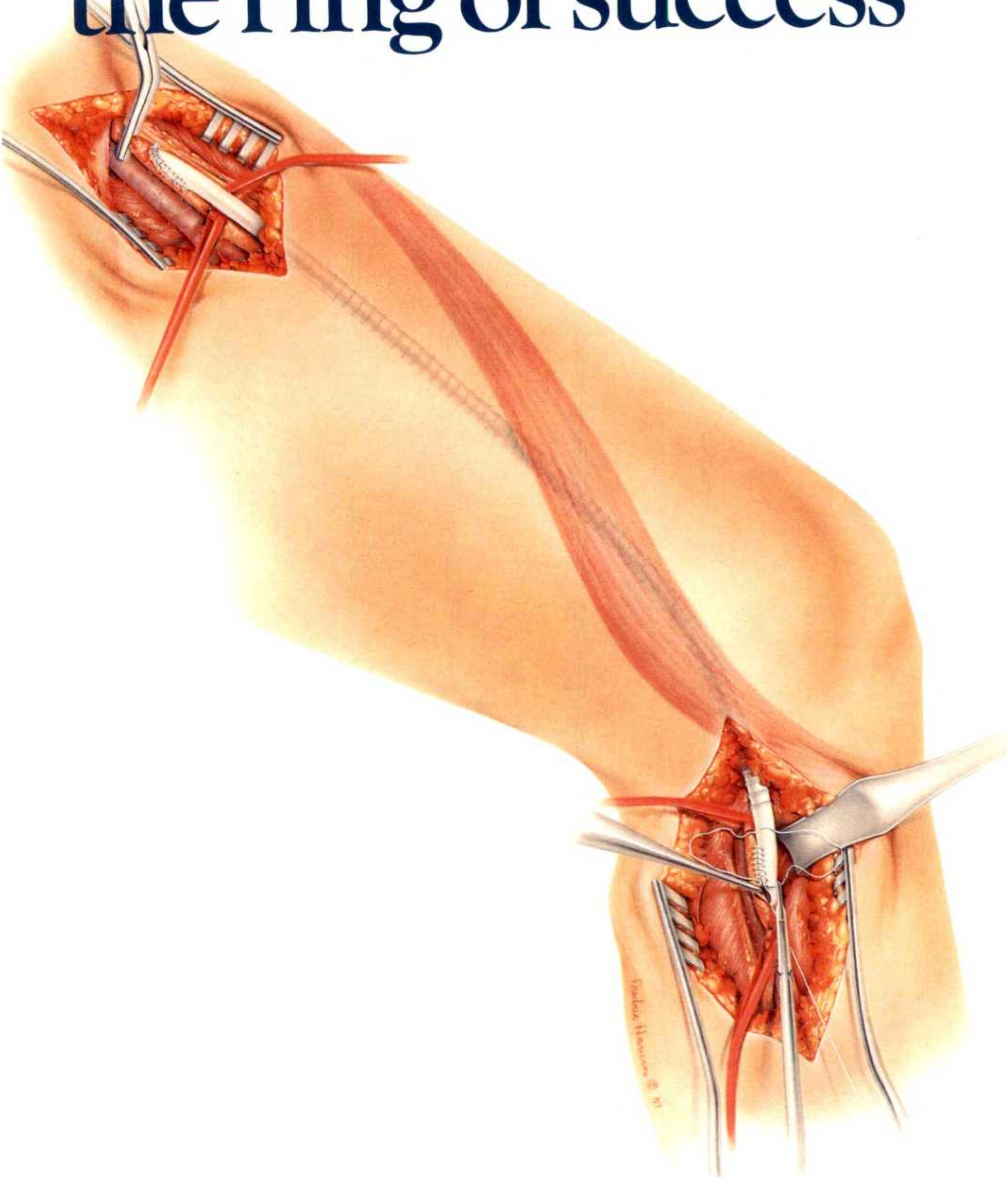

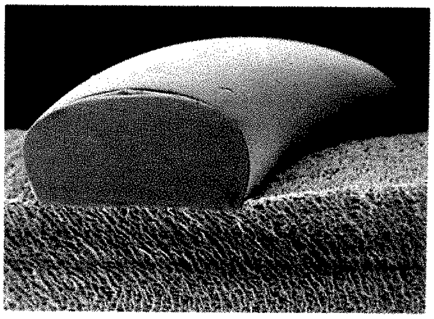

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Contents of Volume 3, Number 1, 1988

	Main topic
Vacanti JP, O'Rourke PP, Lillehei CW, Crone RK	The cardiopulmonary consequences of high-risk congenital diaphragmatic hernia 1
Heaton JFG, Redmond CR, Graves ED, Falterman KW, Arensman RM	Congenital diaphragmatic hernia. Improving survival with extracorporeal membrane oxygenation 6
Frenckner B, Freyschuss U	Pulmonary function after repair of congenital diaphragmatic hernia - a short review 11
Harrison MR	The fetus with a diaphragmatic hernia 15
	Original articles
van der Zee DC, van der Staak FHJ, Severijnen RSVM, Festen C	Proximal fistula in esophageal atresia: Pitfall in a routine procedure 23
Moore S, Millar AJW, Cywes S	Liver abscess in childhood. A 13-year review 27
Spicer RD, Cywes S	Pancreatitis in childhood 33
Peters H. Eißner D, Weitzel D, Dinkel E, Hahn K, Baumann W, Hofmann-v. Kap-herr S	The diagnostic significance of cholescintigraphy and ultrasound examination in cholestatic synchromes in infancy 37
Koloske AM, Jewell PF, Florman AL, Umland ET	Acute abdominal emergencies associated with cytomegalovirus infection in the young infant 43
Slim MS, Fakhri S, Bitar J, Musallam S, Uwaydah M	Acute abdomen in Salmonella infection. Report of ten consecutive cases 47
McMullin ND, Hutson JM, Kelly JH	Minimal surgery in the prune belly syndrome 51
Höllwarth ME, Granger DN Ulrich-Baker MG, Kvietys PR, Ramenofsky ML, Gaginella TS	Pharmacologic enhancement of adaptive growth after extensive small-bowel resection 55
	Technical Innovations
Silverman SH, Stringel G	Two techniques for central catheter placement in the hypogastric and azygos veins 62
	Case reports
Greenholz SK, Karrer FM, Lilly JR	Quadriplegia complicating parenteral nutrition 64
Poenaru D, Laberge J-M, Jéquier S, Blanchard PW, Doody DP	Ultrasound diagnosis of delayed-onset congenital diaphragmatic hernia associated with group B streptococcal infection 66
Janik JS, Hernandez AM, Lilly JR	Esophageal atresia with proximal pouch tracheoesophageal fistula and noncommunicating esophageal duplication 70
Şenyüz OF, Danişmend N. Erdoğan E, Özbay G, Büyükünal C	Total intestinal aganglionosis with involvement of the stomach 74
El-Gohary MA, Sedaghatian R, Mohyuddin Z, Lakshmi B	Separation of xipho-omphalopagus twins 76
Chang KW, Ch'ng SL, Lin HP	Recurrent ganglioneuroblastoma with loss of secretion of vasoactive intestinal peptide and 4-hydroxy-3-methoxy mandelic acid 79

Indexed in Current Contents

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Management of pleomorphic adenoma of the parotid

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A series of 336 parotidectomies, carried out for benign disease has been followed for up to 20 years. One hundred and thirty primary pleomorphic adenomas were treated by wide excision of the tumour after identification of the facial nerve. Recurrence occurred in only one patient and, although 20 patients (15 per cent) experienced some degree of facial nerve weakness postoperatively, there was only one case of permanent weakness.

Keywords: Parotid gland, pleomorphic adenoma, surgical excision

Before 1950 the management of parotid tumours was confused and unsatisfactory, mainly because of fear of damage to the facial nerve. It was recognized that the commonest tumour, pleomorphic adenoma, frequently recurred after surgery and appeared to be radio-resistant. The pathology at this time was ill understood and the tumour was thought by some pathologists to be a well-differentiated carcinoma[1]. However, McEvedy[2] in 1934 had already noted that pleomorphic adenomas were benign and only occasionally underwent malignant change.

In 1940 Patey[3] recognized that the frequent recurrence after enucleation was the result of capsular defects but found that wide excision always resulted in facial nerve destruction. However, in 1941 Bailey[4] stressed the importance of removing the capsule of the tumour after enucleation and went on to describe the anatomy of the seventh nerve in the gland and suggest a form of conservative wide excision of parotid tumours. By 1954 Patey[5] had fully defined and described conservative and radical parotidectomy. The operation was described in detail in 1957 (reference 6) and, after a 6-year study of 79 parotid tumours[7], the policy of management of pleomorphic adenomas and other tumours was established. While this policy has been generally adopted, many retrospective surveys over the last 20 years[8–11] indicate that enucleation is still being carried out. Despite statements to the contrary[12], there is no doubt that late recurrence of pleomorphic adenoma does occur[13–15] and follow-up of the series to be presented has been delayed until a maximum of 20 years follow-up was achieved.

The complications of superficial parotidectomy include postoperative haematomas, Frey's syndrome, sialoceles, fistulae and neuromas of the great auricular nerve, as well as permanent damage to the facial nerve. It is said that enucleation of parotid tumours results in fewer complications and less risk of damage to the facial nerve[16,17]. The complication rate in the present series of patients treated by wide excision is reviewed in this paper.

Patients and methods

A prospective survey of the results of parotidectomy was started in 1967. All tumours were removed by wide resection after identification and preservation of the facial nerve and its branches if this was possible without breaching tumour tissue[18,19]. All patients with pleomorphic adenoma were followed yearly with instructions to report earlier if they had any cause for concern about the results of the operation.

A personal series of 336 parotidectomies were carried out for benign disease, of which 208 were conducted for benign neoplasms (*Table 1*); 156 pleomorphic adenomas were treated of which 26 were recurrent, leaving 130 primary pleomorphic adenomas. Of the 130 patients with primary pleomorphic adenomas, 10 died at varying intervals during the 20-year follow-up without recurrence of their tumour. A total of 6 patients were lost to follow-up; 114 patients were successfully followed (*Table 2*) and there was one recurrence at 11 years after the primary operation. There were 69 women and 61 men; their ages ranged from 13 to 92 years.

Results

The series of 130 patients undergoing parotidectomy for primary pleomorphic adenoma was reviewed with respect to immediate and late postoperative complications. There were no postoperative deaths. As already indicated, one recurrence occurred 11 years after operation in a 29-year-old woman and comprised a 0·7 cm nodule in the skin just below the scar at the angle of the jaw. There has been no further recurrence in the succeeding 2 years. The original tumour measured 4 cm in diameter and was in the deep lobe of the gland. The capsule was found to be ruptured at the time of operation and the wound irrigated with sterile water. Radiotherapy was not considered in view of her age.

Evidence of facial nerve damage was found in the immediate postoperative period in 20 patients and most frequently involved movement of the lower lip only. There was one case of permanent weakness of the lower lip which has persisted 4 years after operation and obviously will not now recover. However, this patient was a 34-year-old woman who had undergone a superficial parotidectomy on the same side 9 years previously for recurrent parotid obstruction and painful swelling of the gland. The primary tumour had developed in the deep lobe remnant. There is one further patient with facial nerve weakness of the lower lip within 1 year of operation, who may yet recover (*Table 3*).

Capsular rupture occured in eight operations, mainly in patients with deep lobe tumour. In the early 1970s these patients had radiotherapy and the operation site was irrigated with sterile water. Latterly, irrigation only was used, in view of the possible danger attached to radiotherapy; one of these cases was the only recurrence in this series.

Postoperative haematoma necessitated immediate return to

Table 1 *Parotidectomy for 336 benign conditions of which 208 were benign neoplasms*

Pleomorphic adenoma—primary operation	130
Recurrent pleomorphic adenoma	26
Adenolymphoma	37
Lipoma	13
Neurofibroma	2

Table 2 *Primary parotidectomies (114) for pleomorphic adenoma followed up for a maximum of 20 years*

Follow-up period (years)	No. of operations
16–20	13
11–15	15
5–10	35
<5	51

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Table 3 *Facial nerve damage following parotidectomy in 130 cases*

	Immediate postoperative weakness	Permanent weakness
Lower lip	14 (1 persists at 1 year)	1 (previous parotidectomy for inflammatory disease)
Upper lip	1	
Nose	1	
Eyebrow	2 (1 occurred after removal of suction drain)	
Eye	1	
Complete	1	
Total	20 (15%)	

Recovery of postoperative facial nerve palsy took between 1 month and 2 years

theatre and evacuation of the clot in one case. A collection of saliva under the wound occurred in four cases and all resolved within 4 weeks with repeated aspiration. One patient developed a salivary fistula through the wound which healed spontaneously within one month. Radiotherapy was not used in any of these cases.

There were no neuromas of the greater auricular nerve. Frey's syndrome of gustatory sweating developed in 22 patients but is mild in all cases and, once explained to the patient, of no concern[20,21]. Tympanic neurectomy has not been necessary (reference 22 and P. H. Golding-Wood, personal communication). Two patients developed keloid scars.

Discussion

All benign parotid tumours in the superficial lobe present as a lump and, unless there are clinical signs suggesting malignancy, accurate pre-operative diagnosis of the nature of the lump is not possible. About 10 per cent of tumours occur in the deep lobe or extend deeply; oral examination should always be carried out and ideally bimanual examination of the faucial region should be performed[23]. Further investigations are unnecessary in most cases. Sialography does not help in the diagnosis[24-26] but ultrasound may, in the future. In deep lobe tumours, particularly those presenting as diffuse enlargement of the gland, CT scanning has proved to be a major advance in investigation and is invaluable in the management of malignant tumours[27]. Radioisotope scanning may allow intelligent guesses as to the histology of a parotid mass but does not preclude the need for excision for histology. Needle biopsy has not been used in this series, partly because of the difficulty sometimes encountered in accurate histological diagnosis of the whole tumour, let alone a small biopsy, and because of the risk of seeding tumour along the needle track[11,28,29]. In short, the principle that all lumps in the parotid gland should be widely excised has been adhered to in this series[24,30]

The surgical approach was the same throughout and has been detailed elsewhere[18,19]. The method is essentially the same as that described by Patey[6] and involves identification of the facial nerve 1 cm anterior to the posterior border of the parotid and well clear of the tumour. Centripetal dissections of the facial nerve have been advocated[31]. Dissection begins opposite the V sulcus made by the anterior border of the mastoid process and the external auditory meatus[32]. Usually a major branch of the nerve beyond its main trunk is identified and a wide resection of the tumour is carried out with a generous surrounding cuff of normal parotid. A formal total superficial parotidectomy seems unnecessary and increases the risk of damage to the fine branches of the facial nerve as they leave the anterior and superior borders of the gland[33]. There are no reported cases of multicentricity of tumours of the parotid, with the exception of adenolymphoma which is benign and does not recur[1,7,34].

In many patients, however, part of the tumour had breached the confines of the gland and the dissection must then necessarily be carried out close to the tumour. This is particularly so in deep tumours[35]. In many patients one or more branches of the facial nerve were closely attached to the capsule but were easily dissected by sharp dissection without breach of the capsule[36]. As the latter is often incomplete histologically it seems wise in such cases to irrigate the site with sterile water but probably unwise to use stronger agents[6,37]. It is essential to avoid capsular rupture and spillage of tumour as this increases the risk of recurrence, as in the recurrence reported here and in the series of Hobsley[38].

There still seems to be controversy regarding the correct method of surgical treatment of parotid tumours. Wide excision after nerve dissection is now probably the commonest procedure but enucleation alone or followed by radiotherapy is still being advocated. It is not clear in many papers on this subject what precisely is meant by enucleation. Historically, enucleation was considered to be the simplest way to avoid facial nerve damage[3] and in the first half of this century the capsule of the tumour was opened and the contents aspirated. It was then realized that recurrence was too frequent and it became the practice to aspirate and then to excise the collapsed capsule[4]. Finally, enucleation came to mean extracapsular dissection and removal of the whole tumour. In various series of cases, postoperative radiotherapy or radium implantation was employed in the theoretical belief that it decreased the recurrence rate.

In most papers comparing enucleation with superficial parotidectomy or wide excision following nerve dissection, the recurrence rate in the former is high, but the complication rate of surgery is low. Maimaris[11] described six recurrences in 49 enucleations for pleomorphic adenoma compared with no recurrences in 42 superficial parotidectomies in a 6–20-year follow-up. Woods[1] reported 824 operations for pleomorphic adenoma with an 8 per cent recurrence rate following enucleation compared with 2 per cent following superficial parotidectomy. In another series[34], Frey's syndrome occurred in 20 per cent of patients after superficial parotidectomy and not at all following enucleation. In contrast, in 5 per cent of patients whose tumours were enucleated, permanent facial nerve damage occurred, but this complication was found in only 3 per cent of superficial parotidectomies. Haw[39] reported 18 patients undergoing superficial parotidectomy for primary pleomorphic adenoma, of whom 6 had permanent nerve damage and 8 developed Frey's syndrome. In contrast, he reported nerve damage in only 3 of 50 patients having enucleation for primary pleomorphic adenoma, and no case of Frey's syndrome.

Many of these observations are retrospective and it is difficult to draw a firm conclusion as to their significance. A number of different surgeons were involved and the details of the operations are unknown[40,41].

In Gleave's follow-up of 369 primary pleomorphic adenoma patients[33], there is no doubt as to the type of operations performed; meticulous extracapsular dissection in 257 cases is compared with 112 superficial parotidectomies. The recurrence rate is almost identical, that is 1·9 per cent for extracapsular dissection and 1·8 per cent for superficial parotidectomy, and there seems nothing to choose between the two operations. There was permanent seventh nerve damage in only 6 of the 369 cases but the type of operation is not distinguished. Radiotherapy was not given routinely to patients undergoing primary surgery.

Other authors during the last few years have advocated enucleation with postoperative radiotherapy to decrease the risk of recurrence although the complication rate has seemed no different to that following superficial parotidectomy. Van Miert[42] in 183 cases of primary enucleation and postoperative radiotherapy for pleomorphic adenoma reported recurrence in 5 patients (2·7 per cent) and permanent facial palsy in 12 (6·5 per cent) cases.

McEvedy in 1976 (reference 10) reported on the follow-up of 73 pleomorphic adenoma patients treated by enucleation and radiotherapy for between 5 and 12 years. There were two (2·7 per cent) recurrences and permanent facial nerve damage in four (5·4 per cent) patients. The follow-up period may not be long enough. Armistead[12] reported a series of extracapsular dissections in 76 patients followed by postoperative radiotherapy. More than one-half of the patients were followed for over 10 years, and some up to 16 years. There was only one recurrence and one permanent nerve palsy. However, in 16 cases there was capsular rupture during the operation, which may perhaps have been salvaged by postoperative radiotherapy.

There is indirect evidence that radiotherapy for benign tumours may not be justified because of the risk of induced malignancy. Hazen[43] compared 971 children between 5 and 14 years of age, who had head and neck irradiation, with 2746 untreated siblings. In the irradiated group 13 neoplasms developed (0·013 per cent) of which 2 were salivary gland tumours and 3 thyroid tumours. In the untreated group 33 neoplasms (0·012 per cent) occurred but no salivary or thyroid tumours. Modan[44] in 1979 reported 10920 patients who were irradiated for ringworm of the head and compared them with 16000 non-irradiated controls and siblings. In the irradiated group four malignant parotid tumours and three benign tumours developed while only one benign parotid tumour developed in the controls. Schneider[45] reviewed 1922 children who had had radiotherapy for tonsil and adenoid enlargement. A total of 17 pleomorphic adenoma and 9 malignant parotid tumours developed subsequently, giving an overall instance of $770/10^6$ population compared with the normal instance of $11/10^6$ in the United States. They further noted that the development of new tumours was not declining 35 years after irradiation.

Many other papers have drawn attention to the potential risk of irradiation of salivary tissue[46-48] and the facial nerve[49,50]. This subject was carefully reviewed recently by Watkin and Hobsley[51] and the dubious value and definite disadvantages of radiotherapy for mixed salivary tumours after enucleation is discussed by the same authors[52].

It is generally agreed that the correct treatment for early malignant parotid tumours and the rare slowly growing tumours such as acinic cell and low-grade muco-epidermoid tumours is wide excision. As it is impossible to distinguish such tumours from the much commoner pleomorphic adenoma[7] it seems reasonable to advocate wide resection of all apparently benign parotid tumours after nerve dissection, and to avoid capsular rupture at all costs. It does not seem justifiable to irradiate benign tumours to salvage the results of more conservative surgery designed to decrease the complication rate. The risk of recurrence is less after wide resection in most recorded series and the risk of permanent facial nerve damage is low. The high rate of Frey's syndrome has to be accepted and most patients tolerate the minor inconvenience.

Finally the risk of permanent seventh nerve damage is much higher in operations for multicentric recurrent pleomorphic tumours, as is the risk of yet further recurrence. The best operation for pleomorphic adenoma is the first. It is our routine practice to see patients regularly once a year for the rest of their lives, given that late recurrence may occur[12-14,20,42,53].

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Joint Meeting of Surgical Colleges

Progress report on Intercollegiate Specialty Assessment

The four Royal Surgical Colleges in Great Britain and Ireland have, over the past 3 years, been giving earnest consideration to the need to make assessment of training in all the specialities of surgery more relevant to the demands of surgical practice now and in the years ahead. Much has been achieved by the collaborative work of the Joint Committee on Higher Surgical Training since 1967. That committee, representing the Surgical Colleges, the surgical specialist associations, and the Professors of surgery, has set the pattern in devising surgical training programmes at senior registrar level which give to the trainees experience of a wide range of clinical work at university and district general hospitals over minimum periods of 3–4 years according to the specialty.

Increasingly the Joint Committee has recognized the need to assess not only the quality of the training programmes but the extent to which those who occupy them have made the best use of the opportunities they offer. The four Colleges therefore decided the time had come to introduce a means of formal assessment of specialist trainees. Such intercollegiate assessments have been designed to establish not only the standard of performance of trainees but also the extent to which they have kept themselves up to date in studying the current literature. Assessments were introduced last year in plastic surgery and in urology and have taken the form of in-depth oral discussions of those aspects of the specialty with which the senior registrar or lecturer in the second or third year of a higher training programme should be familiar. The assessments have been held on a voluntary basis but, after some initial hesitation, most higher trainees have submitted themselves as candidates and most have been successful at the first attempt. Discussions are now in hand to introduce similar assessment procedures in general surgery and in the other specialties including those for which the Edinburgh College has introduced specialty Fellowship examinations almost a decade ago (orthopaedic surgery, neurological surgery and cardiothoracic surgery). It is anticipated that the experience gained through these intercollegiate assessments will facilitate an improved review of the training programmes.

Concurrently with this initiative the four Surgical Colleges are studying a revision of their existing Fellowship examinations with a view to adapting them to a new continuum of postgraduate surgical examination and assessment and in order to make them more relevant to future surgical practice. While there is no intention of making the present Fellowships intercollegiate—indeed the Colleges are anxious to preserve the identity of their own Fellowships and believe that there is value in that degree of diversity—they are keeping in close touch with each other to ensure that the standards of the four Fellowships remain comparable. The common objective will be to develop reciprocally recognized Fellowship examinations of a high standard in the basic sciences relevant to modern surgery and in the basic surgical principles that are necessary for entry to higher training in each and every surgical specialty. The diplomas of Fellowship will have reciprocal status and, after further specialty training, will permit entrance to the Intercollegiate Board Assessment procedure.

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Value of the tympanomastoid fissure in the exposure of the facial nerve

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Should the surgeon elect to identify the main trunk of the facial nerve at an early stage in the operation of superficial parotidectomy, the tympanomastoid fissure (TMF) is an invaluable guide to the nerve. The fissure receives no mention in a classical monograph of human osteology[1], and it is also not referred to in some standard works of operative surgery[2]. In other publications it is mentioned, but perhaps is insufficiently stressed[3].

Figure 1 is a photograph of the relevant area of the base of the skull, and illustrates the TMF. After the usual wide mobilization of the posterior surface of the parotid from the sternomastoid muscle, the gland is retracted forward and the TMF can be identified anterior to the mastoid process (*Figure 1*, 2 and 3). Initially it can be readily palpated with the gloved index finger, then seen as mobilization proceeds. As indicated by the arrow (*Figure 1*, 2), the TMF when followed medially leads directly to the stylomastoid foramen (*Figure 1*, 5), through which the nerve emerges.

As the incision is deepened the vaginal process of the tympanic bone can again initially be felt, then clearly seen, forming the anterior boundary of the TMF (*Figure 1*, 9).

A useful landmark for the depth at which the nerve will be found is the deep surface of the posterior belly of the digastric muscle, arising as it does from the groove for the posterior belly of that muscle (*Figure 1*, 8), deep to the mastoid process (*Figure 1*, 3).

It is my belief that a modest degree of magnification (Zeiss operating spectacles × 2·5) greatly facilitates the deeper dissection. This magnification allows the small veins that run on the surface of the nerve to be readily seen. These veins further assist in the identification of the nerve, and help to distinguish between the nerve and multiple strands of connective tissue which require division as the gland is mobilized.

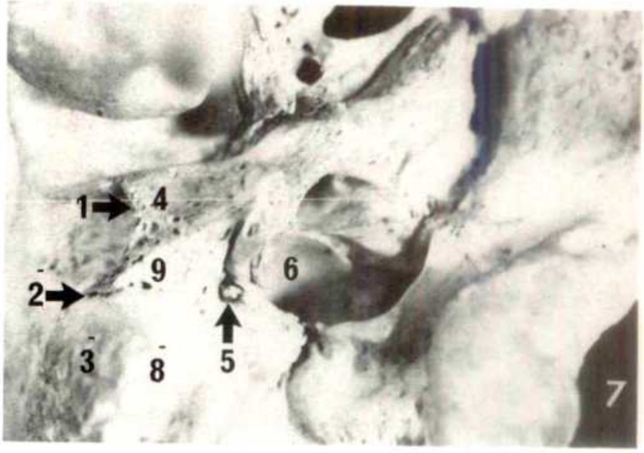

Figure 1 *Illustration of the base of the skull to show the tympanomastoid fissure. 1, External auditory meatus; 2, tympanomastoid fissure (TMF); 3, mastoid process; 4, tympanic plate; 5, stylomastoid foramen; 6, jugular foramen; 7, foramen magnum; 8, groove for posterior belly of digastric; 9, vaginal process of temporal bone. (All names except TMF from Frazer*[1]*). The TMF (2) at the anterior surface of the mastoid process (3) leads directly to the stylomastoid foramen (5). The fissure, the direction of the fissure, and the position of the stylomastoid foramen are also indicated by arrows. The nerve lies at the same depth as the deep surface of the posterior belly of the digastric muscle (8)*

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Intraparotid anatomy of the facial nerve and retromandibular vein

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Fifty-four cadaver dissections of the parotid gland and the extracranial course of the facial nerve were made. In 52 out of 54 specimens dissected (96·3 per cent) the retromandibular vein was present and of significant calibre (> 2 mm). In all specimens the main facial nerve trunk or its major divisions were in direct contact with the retromandibular vein at the level of its entry into the parotid gland. This finding is discussed in the context of new developments in body scanning techniques and put forward as a potential adjuvant in the clinical management of lumps in the parotid region.

Keywords: Facial nerve, retromandibular vein, parotidectomy, magnetic resonance imaging

The course of the facial nerve (nervus facialis) within the substance of the parotid gland (glandus parotidea) is of interest to surgeons because of its vulnerability during operations to remove tumours within the gland, particularly if such a tumour lies deep to the nerve. Pre-operatively there is no way of accurately predicting the relationship of a tumour to the nerve unless paresis is already present, or unless a tumour lying at least partially deep to the nerve is seen to bulge the wall of the pharynx medially in the region of the tonsillar fossa. The surgeon may unexpectedly find that damage to the nerve is inevitable in order for the tumour to be removed in its entirety. It is thus standard practice to warn any patient undergoing surgery to the parotid gland of this risk, although the chances of damage vary greatly depending on whether the tumour is malignant or benign and whether the tumour lies superficial or deep to the nerve.

The gland substance is often regarded as being divided into two lobes by the nerve[1] but it has been demonstrated that the relationship of the gland tissue to the nerve is variable with no true anatomical division into lobes[2]. Instead, the salivary tissue tends to invaginate the nerve in a random fashion and no readily dissectable surgical plane exists between superficial (pars superficialis) and deep parts (pars profunda) of the gland. Moreover, the exact relationship of the nerve to the retromandibular vein (vena retromandibularis) is given scant attention in most standard anatomical texts[3–5]. The close relationship between retromandibular vein and external carotid artery (arteria carotis externa) is widely documented. As modern imaging techniques have made it possible to visualize vascular structures without the use of radio-opaque contrast media, the importance of these structures as landmarks is greatly increased.

This paper sets out to define the relationship between the facial nerve and retromandibular vein within the parotid gland and thus to establish the value of the vein as a marker for the nerve. Assuming a constant relationship, it might be possible, by carrying out a single scan of the area, to establish whether a tumour lies superficial or deep to the nerve. A better pre-operative assessment of the risk to the nerve could then be made and the likely technical difficulty of the procedure established.

Materials and methods

In all, 54 dissections were performed by the authors on the parotid gland of 31 cadavers. Bilateral dissections were performed on 24 cadavers, left-sided only on 5 and right-sided only on 1.

Removal of the skin and superficial tissues was carried out by medical students, exposing the parotid gland but leaving it intact.

The dissection technique involved finding the superficial temporal vein (vena temporalis superficialis) and tracing it inferiorly to its confluence with the maxillary vein (vena maxillaris) within the parotid gland. The retromandibular vein, so formed, was followed until the main facial nerve trunk or its primary divisions were encountered. Dissection of the remaining length of the vein and branches of the nerve was continued until the relationship between the vein and all branches of the nerve was clearly displayed.

Specimens where no satisfactory demonstration of the nerve or vessel was possible due to previous dissection, or in poorly preserved cadavers, were excluded from the study.

Results

In 52 out of 54 specimens dissected (96·3 per cent) the retromandibular vein was present and of significant calibre (>2 mm). Thirty-seven specimens (68·5 per cent) showed the pattern shown in *Figure 1a* and *b*. The division of the main trunk was within 5 mm of the retromandibular vein and both upper and lower divisions were in direct contact with, and superficial to, the vein.

Eleven specimens (20·4 per cent) showed the pattern illustrated in *Figure 1c*. Here the division of the main trunk was within 5 mm of the retromandibular vein and the upper division was in direct contact with the vein and superficial to it. The lower division, however, tended to diverge superficial to the vein with a small amount of parotid tissue intervening.

Five specimens (9·3 per cent) showed the pattern seen in *Figure 1d* (and see *Figure 2*). Here the confluence of the superficial temporal and maxillary veins to form the retromandibular vein occurred at a more inferior level. The upper division of the main trunk divided to run both deeply and superficially to, but in close contact with, the two tributaries of the vein and the lower division was in contact with the main vein.

One specimen (1·8 per cent) showed the pattern seen in *Figure 1e*. Here the main trunk divided in the standard manner but the lower division travelled deep to the vein although in direct contact with it.

Discussion

It is widely recognized that, apart from failure to achieve adequate tumour clearance, one of the main hazards of operating on pathological lesions in the parotid gland is the risk of damage to the facial nerve. The anatomy of the extracranial course of the nerve is documented in detail in most anatomical texts and works on surgical anatomy but emphasis is given to the relationship of the main trunk to the gland itself and to the pattern of its division. McCormack and co-workers (1945) dissected 100 cadavers and categorized them according to the pattern of branching and to the major anastomosis found between branches[6]. Mention is made that the nerve runs superficial to the external carotid artery and retromandibular

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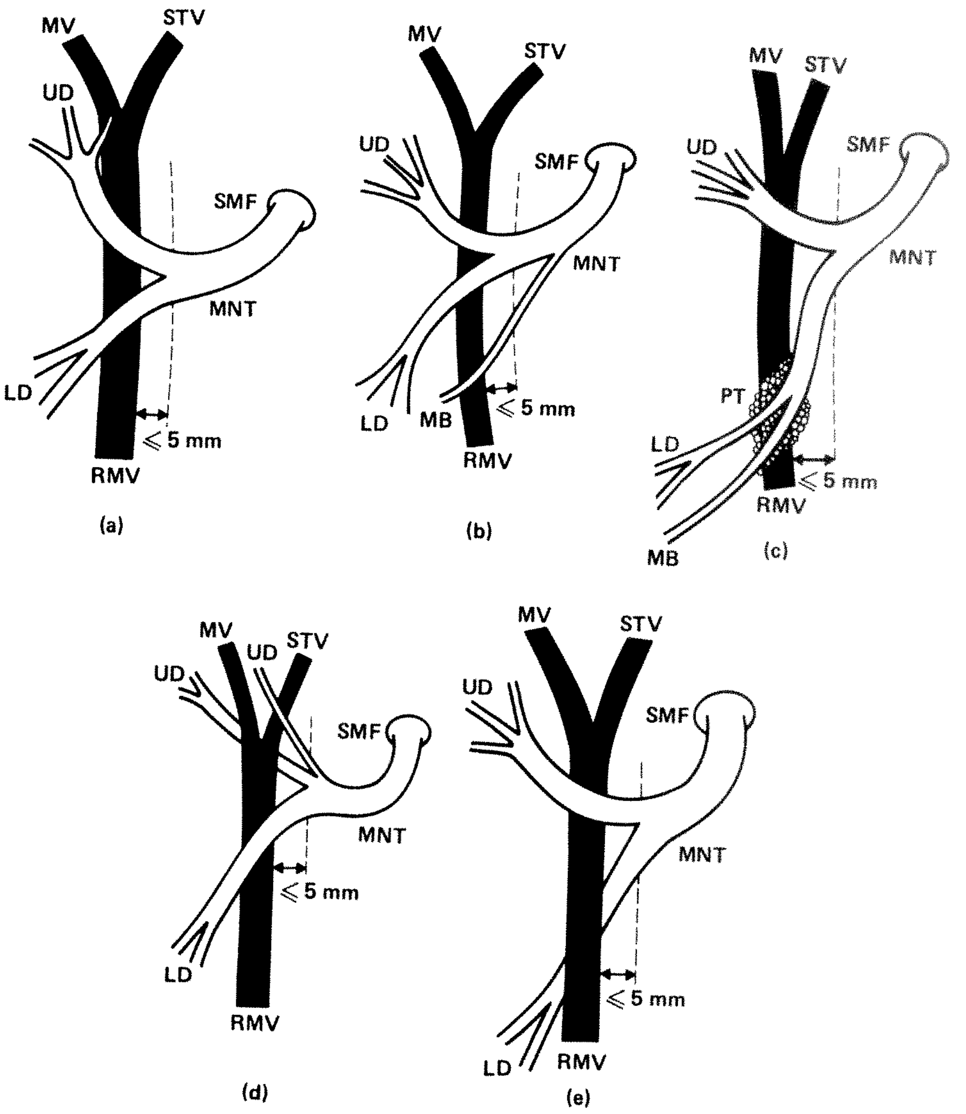

Figure 1 *The relationship of the facial nerve to the retromandibular vein (left side). SMF, Stylomastoid foramen; MNT, main nerve trunk; STV, superficial temporal vein; MV, maxillary vein; RMV, retromandibular vein; UD, upper division; LD, lower division; and PT, parotid tissue*

vein, but the exact relationship of the nerve trunk and its branches to the vein is not documented in detail in any of the commonly used textbooks of surgical anatomy[7-10]. Beahrs and Adson (1958) make the point, in their paper on the surgical anatomy and technique of parotidectomy, that the vein lies in the same plane as the facial nerve[11]. They also state that the cervical branch of the nerve often overlies the vein but do not discuss the relationship in any greater depth.

Recent developments in non-invasive imaging of this region, using the technique of magnetic resonance imaging (MRI), have made this relationship between nerve and vein of much greater potential significance. The technique permits consistent visualization of the vascular bundle constituting retromandibular vein and external carotid artery at the level of the main facial nerve trunk. This ability is likely to be enhanced as the resolution of MRI improves and it therefore seems probable that the position of these vessels within the parotid substance is of greater importance as a landmark than was previously realized (*Figure 3*).

The present series of 54 dissections has demonstrated a constancy in the presence and calibre of the retromandibular vein. A consistent relationship also appears to exist between the vein, the main nerve trunk and its major divisions. Variations in the anatomy of the nerve, vein, and in the relationship between them constitute only a small percentage of the total (11·1 per cent) but the main principle of intimate contact between vein and nerve is virtually constant.

These findings, together with the reliable visualization of vessels by MRI scanning, have important clinical implications. There may now exist a means of predicting, with accuracy, the location of a mass in the parotid region, with reference to the facial nerve. Even failure to visualize the vessels by scan should be significant, indicating pressure occlusion by a mass lying in close proximity to the vein and hence the nerve trunk itself.

It should be stressed that information gained from pre-operative scanning, no matter how accurate, will never be a substitute for experience in parotid surgery and a sound knowledge of the surgical anatomy. Most lumps in this area should be excised with a wide margin of normal tissue. The facial nerve and its branches should be preserved, provided this is technically compatible with tumour clearance.

We would hope nevertheless that information gained from pre-operative MRI scanning may help to minimize the unpleasant surprises sometimes associated with surgery in this region and so prepare both surgeon and patient more completely and safely.

Clinical experience should establish its eventual place in the diagnostic armamentarium.

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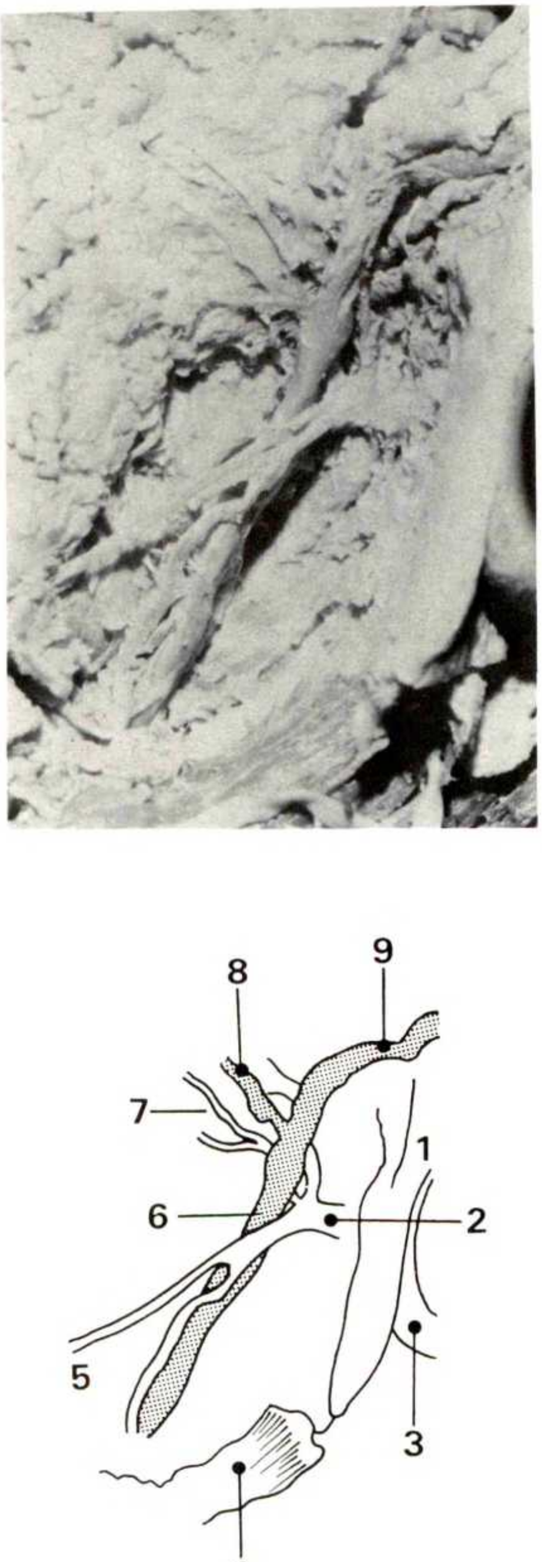

Figure 2 *Photograph and illustration of the dissection on the parotid gland (left side as in* Figure 1d). *1, Skin flap; 2, main facial nerve trunk; 3, auricle; 4, masseter; 5, lower divisions; 6, retromandibular vein; 7, upper divisions; 8, maxillary vein; and 9, superficial temporal vein*

advice. Thanks also to the Department of Anatomy (Aberdeen University) and its students for their co-operation.

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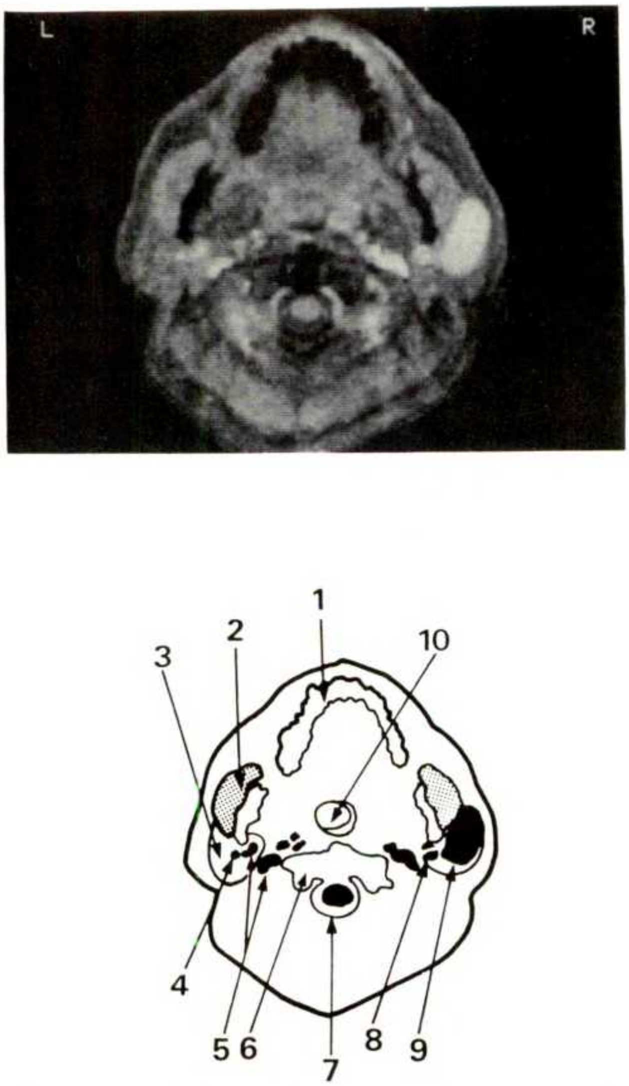

Figure 3 *Calculated T_1 magnetic resonance image made using an inversion recovery pulse sequence of $T^R = 1000$ ms; TI = 200 ms. Subcutaneous fat appears dark grey, muscle appears light grey and blood vessels are white. (T_1, proton spin-lattice relaxation time; T^R, repetition rate; TI, inverting pulse.) The illustration indicates 1, mandible; 2, masseter; 3, parotid; 4, retromandibular vein; 5, internal jugular vein and carotid vessels; 6, first cervical vertebra; 7, spinal cord; 8, retromandibular vein and external carotid; 9, parotid tumour; and 10, pharynx/uvula*

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Short note

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Incidence and diagnosis of parotid gland tuberculosis in Asians in Leicester

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Recent years have seen a decline in the incidence of tuberculosis in Britain, though it remains relatively common in the Asian population. Tuberculosis of the parotid gland is rare, but a recent report from Leicester described its occurrence in an Asian patient[1]. As Leicester has a large Asian community, we investigated the relative incidence of tuberculosis of the parotid in this area and found a further four cases, all in Asians.

Between January 1982 and February 1987, 191 patients with localized parotid swellings presented to Leicester hospitals. The histopathology reports were examined and Asian patients were identified by their surnames.

Results

There were 14 Asian and 177 non-Asian patients and the pathology in the two groups is compared in *Table 1*. In the Asian group the joint commonest causes of parotid swelling were pleomorphic adenoma and tuberculosis (28·6 per cent each), followed by adenolymphoma (14·3 per cent). Pleomorphic adenoma (49·2 per cent) and adenolymphoma (11·3 per cent) were the most common pathologies in the non-Asian group. Tuberculosis was not found in the latter group and the difference in its incidence was significant ($\chi^2 = 38·7$, $P < 0·001$; χ^2 test with Yates's correction).

The Asian patients with tuberculosis of the parotid comprised three men and one woman and ranged in age from 32 to 46 years. They had been in England from 6 months to 18 years. The parotid swellings had been noticed for 2–4 months and were 2–3 cm in diameter. No patient had a previous history of tuberculosis and all had a normal chest radiograph. Two patients underwent superficial parotidectomy on a clinical diagnosis of salivary tumour; histology showed caseating granulomata with Langhans' giant cells, but no specimen had been sent for bacteriological investigation. The other two patients had the swelling aspirated (though it was fluctuant in only one); the aspirates yielded acid/alcohol fast bacilli on microscopy. All four patients received antituberculous chemotherapy and remain well.

Table 1 *Causes of parotid swellings examined in the Department of Pathology, Leicester Royal Infirmary, from January 1982 to February 1987*

	Non-Asians		Asians	
	n	(%)	*n*	(%)
Pleomorphic adenoma	87	49·2	4	28·6
Adenolymphoma	20	11·3	2	14·3
Monomorphic adenoma	5	2·8	0	—
Squamous cell carcinoma	6	3·4	0	—
Adenocarcinoma	9	5·1	0	—
Simple cyst	5	2·8	0	—
Sjogren's disease	4	2·3	0	—
Chronic inflammation (stones)	5	2·8	1	7·1
Pyogenic abscess	1	0·6	1	7·1
Tuberculosis	0		4	28·6
Miscellaneous*	35	19·8	2	14·3
Total	177		14	

* Includes fatty change, normal parotid gland and rare tumours of the parotid gland

Discussion

Tuberculosis of the parotid gland is rare, even in countries where the disease is otherwise rife, and is usually confined to intraparotid lymph nodes[2]. It cannot be distinguished from a parotid tumour on clinical examination so surgical exploration has usually been required for diagnosis[1]. The diagnostic difficulty is well documented[1,3–7] and even at operation the tuberculous lesion is usually considered to be a tumour[4]. Maynard stated that 'there is no way of distinguishing such infections from tumours of the parotid and the diagnosis will always be histological, postoperatively'[2]. Fine needle aspiration has recently been advocated for cytological diagnosis of parotid swellings and appears to be safe[8].

In our study the equal commonest causes of parotid swellings in Asians were tuberculosis and pleomorphic adenoma. Unless an abscess has formed, tuberculosis presents as a firm swelling clinically indistinguishable from a tumour. Generally there is no history of tuberculosis and the chest radiograph may be normal. When tuberculosis of the parotid is a possibility the diagnosis may be made by fine needle aspiration (for bacteriological examination) so avoiding an unnecesssary parotidectomy.

Acknowledgements

We are grateful to the Department of Pathology for providing the histopathology reports and to the surgeons for allowing us to report their cases.

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Risk to surgeons: a survey of accidental injuries during operations

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A survey was conducted with the participation of eight consultant general surgeons, two consultant urologists, four consultant orthopaedic surgeons and four surgical residents to find the incidence of accidental injuries to surgeons and their assistants during operations. Of the total of 2016 operations over a one year period there were 112 reported accidental injuries. These included 107 needle stick injuries, 4 knife cuts and 1 diathermy burn. We found that accidental injuries to surgeons during operations were inevitable.

Keywords: Surgery, accidental injury, virus diseases, occupational, intra-operative complications

Accidental injuries during operations can happen to all surgeons. Transmission of diseases, such as hepatitis B, AIDS (acquired immune deficiency syndrome) and viral haemorrhagic fevers, is a potential danger of such injuries. A survey was designed to find the incidence of accidental injuries to surgeons during operations. The mechanism of these injuries was studied. Factors such as duration of operation, the time of day, and the experience of the surgeons were correlated to the incidence of injury. The anatomical site on the surgeon's body at greatest risk to injury was pinpointed. Comparison of such injuries was made between general surgical, orthopaedic and urological operations.

Materials and methods

The survey was directed to eight consultant general surgeons, four consultant orthopaedic surgeons, two consultant urologists and four surgical residents in Abha General Hospital, Asir Region, Saudi Arabia.

It took the form of reporting all accidental injuries sustained during operations by the surgeon or his assistant. The participating surgeons took full responsibility of unconfidential voluntary reporting of all accidental injuries to themselves and their assistants during operations. When such an injury occurred during an operation a questionnaire was filled in (*Figure 1*) consisting of seven questions, six of which involved ticking blank boxes for appropriate answers. The remaining question asked the name of the operation during which the injury took place. Space was available for adding comments and opinions. The survey started on 1 June, 1986 and continued for one year. The details of all operations were recorded in a separate operation log book for each participating surgeon. The operations during which an accidental injury took place were marked in the log book with an asterisk and the proforma (*Figure 1*) promptly completed. A check was made with the hospital records to avoid missing cases.

All operations were grouped as A, B, and C in accordance with the duration of operation. Group A included operations lasting <45 min; group B, those lasting between 45 and 90 min and group C, those lasting longer than 90 min. All operations were also grouped as I and II in accordance with the time of day when the operation was started. Group I (day) included operations which started between 9 a.m. and 9 p.m. and group II (night) included operations which started between 9 p.m. and 9 a.m. All participating surgeons were right handed. The participants were frequently reminded of the survey at the start of their operating sessions throughout the year to avoid failure to report.

Results (*Table 1*)

The total number of operations performed by the participating surgeons during the year of the survey was 2016. There were 112 reported accidental injuries during these operations (5·6 per cent). Of these, 107 (95·5 per cent) were needle stick injuries, 4 (3·6 per cent) were cuts with a knife and 1 (0·9 per cent) was a diathermy burn.

The total number of general surgical operations by eight consultant general surgeons and four residents in general surgery was 1301 (64·5 per cent of total operations in the survey), 92 accidental injuries were reported (7·0 per cent). The total number of orthopaedic operations by four consultant orthopaedic surgeons was 495 (24·6 per cent of all operations) with 14 (2·8 per cent) reported accidental injuries. Two consultant urologists performed 200 operations (9·9 per cent of all operations) and reported 6 accidental injuries (3 per cent).

There were 64 (57·1 per cent) reported injuries to the left hand of the surgeon and 17 (15·2 per cent) reported injuries to the left hand of the assistant. There were 11 (9·8 per cent) reported injuries to the right hand of the surgeon and 20 (17·9 per cent) reported injuries to the right hand of the assistant.

The exact anatomical sites injured during this survey are shown in *Table 2*. The most vulnerable site for such an injury was the left index finger of the surgeon's hand which was involved in 42 injuries (37·5 per cent). Seventy-five injuries (67 per cent of the total) were sustained by the surgeons as

Figure 1 *Questionnaire used during the survey into accidental injuries to surgeons during operations*

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1. Type of injury.
   Needle ☐ Knife ☐ Diathermy ☐ Any other ☐
   Please specify________
2. The exact site of injury.
   Right hand ☐ Left hand ☐
   Fingers: Index ☐ Middle ☐ Ring ☐ Little ☐ Thumb ☐
   Any other ☐ Please specify________
3. The operation during which the injury took place.________
4. The step of operation during which the injury took place.
   While making the incision ☐ While closing the incision ☐
   Any other step ☐ Please specify________
5. Whether the surgeon or assistant suffered the injury.
   Surgeon ☐ Assistant ☐
6. Who was responsible for the injury. Surgeon ☐ Assistant ☐
7. What steps were taken after the injury: Please tick the correct ones.
   a. Change of gloves ☐ b. Wash hands ☐
   c. Application of antiseptic ☐ d. Squeezing the wound ☐
   e. Was retrospective history taken from the patient after the operation regarding diseases which could be spread by such an injury e.g. hepatitis B. Yes ☐ No ☐
   f. Any other steps ☐ g. No step ☐
   Please specify________

Name of reporting surgeon________
Name of assistant________

Date________

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Table 1 *Summary of results*

Injury details	Number	Percentage
Type of injury		
Needle stick	107	95·5
Knife cut	4	3·6
Diathermy burns	1	0·9
Others	0	0
Step of operation during which injury took place		
While making incision	12	10·7
While closing the wound	85	75·9
Any other step	15	13·4

Table 2 *Site of injury*

	Surgeon		Assistant	
	RH	LH	RH	LH
Dorsal aspect	1	4	3	2
Ventral aspect	10	60	17	15
Thumb	1	5	4	2
Index finger	5	42	7	9
Middle finger	2	5	3	3
Ring finger	2	6	3	2
Little finger	1	4	2	1
Palm	0	2	1	0

RH, right hand; LH, left hand

compared with 37 (33 per cent of the total) sustained by the assistants. The main responsibility for causing such injuries was accepted in 82 injuries (73·2 per cent of the total) by the surgeons and in 30 injuries (26·8 per cent of the total) by the assistants. Longer operations had greater incidence of accidental injuries. There were 25 (22·3 per cent) reported injuries in group A, 35 (31·2 per cent) in group B and 52 (46·6 per cent) in group C.

Of the total of 2016 operations, 1859 (92·2 per cent of total) were performed by consultant surgeons with an average surgical experience of 10 years and 157 operations (7·8 per cent of total) were performed by surgical residents with average surgical experience of 2 years. The length of surgical experience was inversely related to the incidence of accidental injuries. The consultants reported 90 injuries with an incidence of 4·8 per cent as compared with the residents who reported 22 injuries with an incidence of 14 per cent. Reported injuries during the night were marginally greater than during the day. In group I (day) 1673 operations (83 per cent of total) were performed with 91 reported injuries giving an incidence of 5·4 per cent. In group II (night) 343 operations (17 per cent of total) were performed with 21 injuries giving an incidence of 6·1 per cent. More injuries occurred during wound closure than at any other step of the operation (*Table 1*).

This survey indicates that despite the knowledge of participation no significant precautionary step was taken in 84 injuries (75 per cent of the total). Gloves were changed on 28 occasions (25 per cent), the surgeon re-scrubbed on 14 occasions (12·5 per cent) and antiseptic was applied to the site of injury on 13 occasions (11·6 per cent). In only 12 patients (10·7 per cent of the total) was a retrospective history of hepatitis B, or any other disease likely to be spread by this mechanism, taken. In most cases such injuries were considered trivial and disregarded completely.

Discussion

This survey highlights the risk of accidental injuries to surgeons. In 5·6 per cent of operations, there was an accidental injury either to the surgeon or his assistant. This figure is far from comforting when diseases such as AIDS are considered. If the development of antibodies to HIV (human immunodeficiency virus) is a measure of infectivity then accidental needle stick injuries seem to constitute a potential risk[1]. Some 11 per cent of surgical gloves are perforated during surgery, so the surgeon and his theatre nurse seem to be at particular risk[2]. Admittedly there could have been intentional or unintentional under-reporting of accidental injuries during this survey but the results point out that accidental injuries during operations do constitute a risk. Comparative analysis of the three surgical specialties surveyed show a greater risk to general surgeons. This may be due to frequent use of fingers during operations as compared with the no-touch techniques preferred by many orthopaedic surgeons. Many urological operations are endoscopic procedures with less risk of accidental injury to the operator. Fatigue at the end of a long operation and desire to finish the job quickly may be responsible for many accidental injuries as shown by an increased incidence in group C.

We emphasize more awareness among surgeons of the possible hazards of the so-called trivial injuries. We look forward to the availability of routine screening of all surgical patients for HIV and hepatitis B. A surgeon has a duty to the well-being of his patients and to his own well-being.

Hepatitis B is not only transferable from patient to surgeon but is readily transferred from surgeon to patient[3]. Regarding AIDS, the risk of acquiring infection by needle stick injuries is calculated to be <1 per cent; in comparison there is a 35 per cent risk of acquiring hepatitis B from an 'e' antigen carrier by the same route[4]. Chronic persistent and chronic active hepatitis, cirrhosis and hepatocellular carcinoma are legacies of hepatitis B infection. Prevalence of hepatitis B surface antigen in the Saudi Arabian patient population is reported to be 7·3 per cent[5]. This is considerably higher than in the general population or blood donors in the UK, where it is 0·1 per cent, but less than in the Far East, where it is >20 per cent[6]. Among health service staff in England and Wales an increase of infection with hepatitis B virus of 25 per cent has been recorded for 1980–4 over the figure for 1975–9[7]. The annual incidence of infection with hepatitis B virus among laboratory scientific staff, surgeons, physicians and nurses is now 37, 25, 11, and 4 per 100 000 respectively[8].

We were interested to find out the common mechanism of accidental injuries during surgery. The left hand of the surgeon was most frequently injured. Most of the injuries were self inflicted and occurred most commonly during wound closure. Most of the surgeons did not blame any particular type of needle as causing more injuries than others. All surgeons in our survey agreed that most needle stick injuries occurred as the needle emerged from the tissues striking the overlying finger while not under direct vision of the surgeon. This may be due to an error of judgement about the expected site of emergence of the needle on the part of the surgeon or his assistant. Findings of this survey are in agreement with this probable mechanism of injury. On many occasions surgeons blamed inadequate assistance or excessive adipose tissue for causing such injuries. We advise surgeons to be more careful during wound closure. We recommend the use of dissecting forceps rather than fingers for steadying and separating tissues while suturing. Care, experience and good surgical technique can reduce accidental surgical injuries.

Acknowledgements

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Journal abbreviations

Acta Medica Colombia [Acta Med Colomb]
Acta Orthopaedica Scandinavica [Acta Orthop Scand]
Acta Paediatrica Japonica [Acta Paediatr Jpn (Overseas)]
Acta Paediatrica Scandinavica [Acta Paediatr Scand]
Acta Pharmacologica Sinica [Acta Pharmacol Sin]
Activox [Activox]
AIDS: An International Bimonthly Journal [AIDS]
AJR: American Journal of Roentgenology [AJR]
American Family Physician [Am Fam Physician]
American Journal of Cardiology [Am J Cardiol]
American Journal of Clinical Nutrition [Am J Clin Nutr]
American Journal of Diseases of Children [Am J Dis Child]
American Journal of Emergency Medicine [Am J Emerg Med]
American Journal of Epidemiology [Am J Epidemiol]
American Journal of Hospital Pharmacy [Am J Hosp Pharm]
American Journal of Human Genetics [Am J Hum Genet]
American Journal of Medicine [Am J Med]
American Journal of Obstetrics and Gynecology [Am J Obstet Gynecol]
American Journal of Optometry and Physiological Optics [Am J Optom Physiol Opt]
American Journal of Pathology [Am J Pathol]
American Journal of Psychiatry [Am J Psychiatry]
American Journal of Public Health [Am J Public Health]
American Journal of Surgery [Am J Surg]
American Review of Respiratory Disease [Am Rev Respir Dis]
American Surgeon [Am Surg]
Anaesthesia [Anaesthesia]
Anaesthesia and Intensive Care [Anaesth Intensive Care]
Anesthesia and Analgesia [Anesth Analg]
Annals of Clinical Biochemistry [Ann Clin Biochem]
Annals of Clinical and Laboratory Science [Ann Clin Lab Sci]
Annals of Internal Medicine [Ann Intern Med]
Annals of Otology, Rhinology and Laryngology [Ann Otol Rhinol Laryngol]
Annals of the Rheumatic Diseases [Ann Rheum Dis]
Annals of the Royal College of Physicians and Surgeons of Canada [Ann R Coll Physicians Surg Can]
Annals of the Royal College of Surgeons of England [Ann R Coll Surg Engl]
Annals of Surgery [Ann Surg]
Annals of Thoracic Surgery [Ann Thorac Surg]
Annals of Tropical Paediatrics [Ann Trop Paediatr]
Archives of Dermatology [Ann Dermatol]
Archives of Disease in Childhood [Arch Dis Child]
Archives of General Psychiatry [Arch Gen Psychiatry]
Archives of Internal Medicine [Arch Intern Med]
Archives of Neurology [Arch Neurol]
Archives of Ophthalmology [Arch Ophthalmol]
Archives of Otolaryngology—Head and Neck Surgery [Arch Otolaryngol]
Archives of Pathology and Laboratory Medicine [Arch Pathol Lab Med]
Archives of Surgery [Arch Surg]
Archivos de Investigacion Medica [Arch Invest Med (Mex)]
Arizona Medicine [Ariz Med]
Arteriosclerosis: A Journal of Vascular Biology and Thrombosis [Arteriosclerosis]
Australasian Journal of Dermatology [Australas J Dermatol]
Australian and New Zealand Journal of Medicine [Aust NZ J Med]
Australian and New Zealand Journal of Ophthalmology [Aust NZ J Ophthalmol]
Australian and New Zealand Journal of Surgery [Aust NZ J Surg]
Australian Family Physician [Aust Fam Physician]
Australian Journal of Hospital Pharmacy [Aust J Hosp Pharm]
Australian Orthoptic Journal [Aust Orthopt J]
Australian Paediatric Journal [Aust Paediatr J]
Bangladesh Journal of Child Health [Bangladesh J Child Health]
Bibliothek for Laeger [Bibl Laeger]
Biomedical Bulletin [Biomed Bull]
Boletin de la Asociacion Medica de Puerto Rico [Bol Asoc Med PR]
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Bordeaux Medical [Bord Med]
Brain and Development [Brain Dev]
British Dental Journal [Br Dent J]
British Heart Journal [Br Heart J]
British Homoeopathic Journal [Br Homoeopath J]
British Journal of Anaesthesia [Br J Anaesth]
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Canadian Family Physician [Can Fam Physician]
Canadian Journal of Anaesthesia [Can J Anaesthes]
Canadian Journal of Comparative Medicine [Can J Comp Med]
Canadian Journal of Public Health [Can J Public Health]
Canadian Journal of Surgery [Can J Surg]
Canadian Medical Association Journal [Can Med Assoc J]
Canadian Veterinary Journal [Can Vet J]
Cardiovascular Research [Cardiovasc Res]
Central African Journal of Medicine [Cent Afr J Med]
Cephalalgia [Cephalalgia]
Chest [Chest]
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Chinese Journal of Orthopedics [Chin J Orthop]
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Clinical Chemistry [Clin Chem]
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Clinical Diabetes [Clin Diabet]
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Transactions—American Society for Artificial Internal Organs [Trans Am Soc Artif Intern Organs]
Transfusion [Transfusion]
Tropical Gastroenterology [Trop Gastroenterol]
Ugeskrift for Laeger [Ugeskr Laeger]
Ulster Medical Journal [Ulster Med J]
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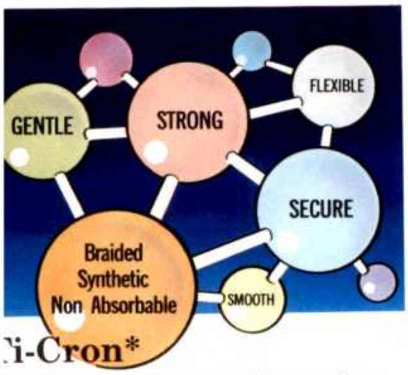

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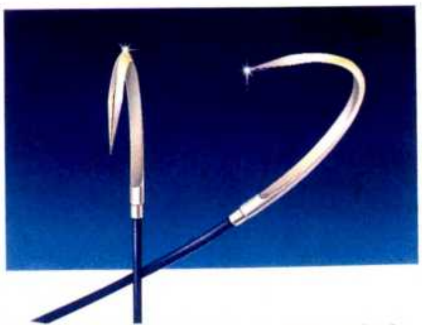

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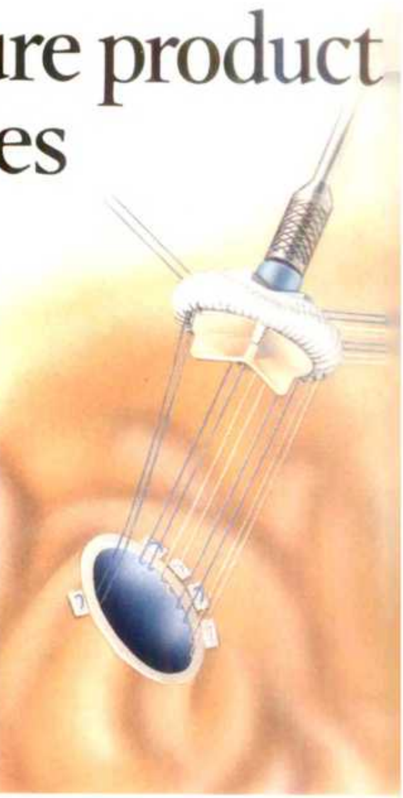

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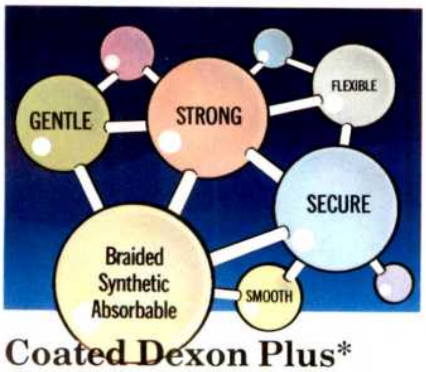

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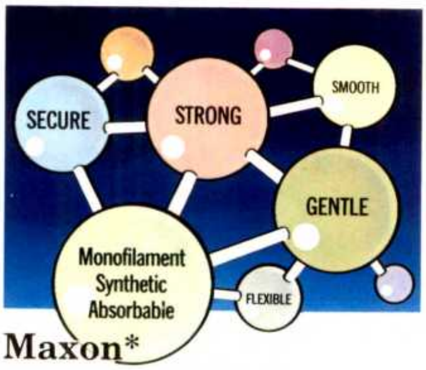

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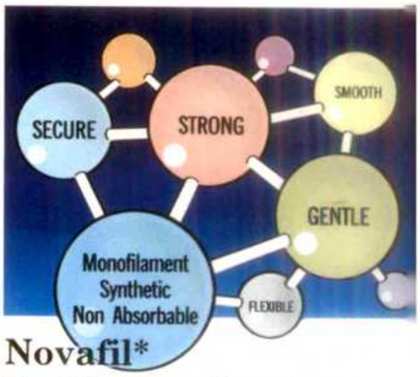

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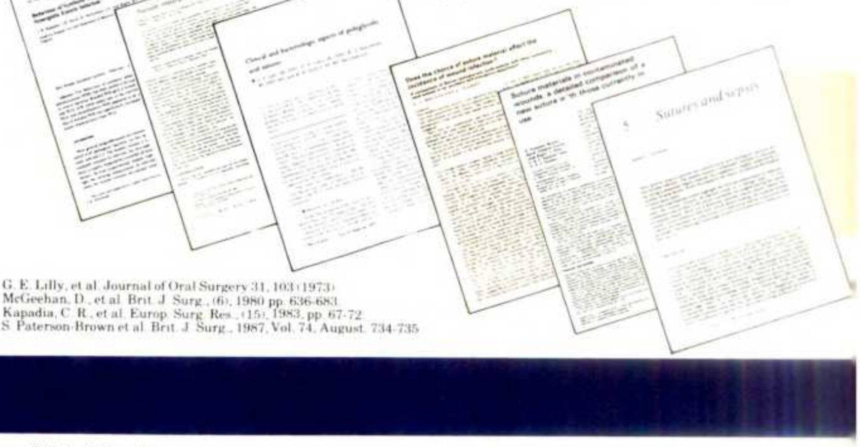
Does the choice of suture material affect the incidence of wound infection?
Suture materials in contaminated wounds: a detailed comparison of a new suture with those currently in use
Sutures and sepsis

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4 S. Paterson-Brown et al. Brit. J. Surg., 1987, Vol. 74, August. 734-735

Softgut - Technical Information
Uses Suturing surgical and traumatic wounds and ligating blood vessels **CONTRA-INDICATIONS** Procedures requiring prolonged wound support **PRECAUTIONS** Discard opened, unused sutures. **SIDE EFFECTS** Tissue reaction or inflammation, occasionally wound dehiscence and bleeding. **LEGAL CATEGORY P. PRESENTATION** Sterile, absorbable, collagen sutures, plain or chromic in packs of one, two or three dozen. PL 0095/0096, PL 0095/0097

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USES Sutures are intended for use where an absorbable suture of ligature is indicated. **CONTRA-INDICATIONS** Where a non-absorbable suture is needed. The safe use of **MAXON** in neural, cardiovascular and ocular tissues has not been established. **PRECAUTIONS** Discard opened and unused sutures. Do not re-sterilise. For absorption data see full data sheet. **PRESENTATION** Sterile synthetic absorbable monofilament sutures. Clear or green sutures in packs of one

Coated Dexon* Plus – Technical Information
USES Suturing surgical and traumatic wounds and for ligating blood vessels. **CONTRA-INDICATIONS** Procedures requiring prolonged wound support. **PRECAUTIONS** Safe use in neural tissue and cardiovascular surgery has not been established. Discard opened unused sutures. For absorption data see full data sheet. **SIDE EFFECTS** Tissue reaction or inflammation, occasionally wound dehiscence and bleeding. **LEGAL CATEGORY P. PRESENTATION** Sterile.

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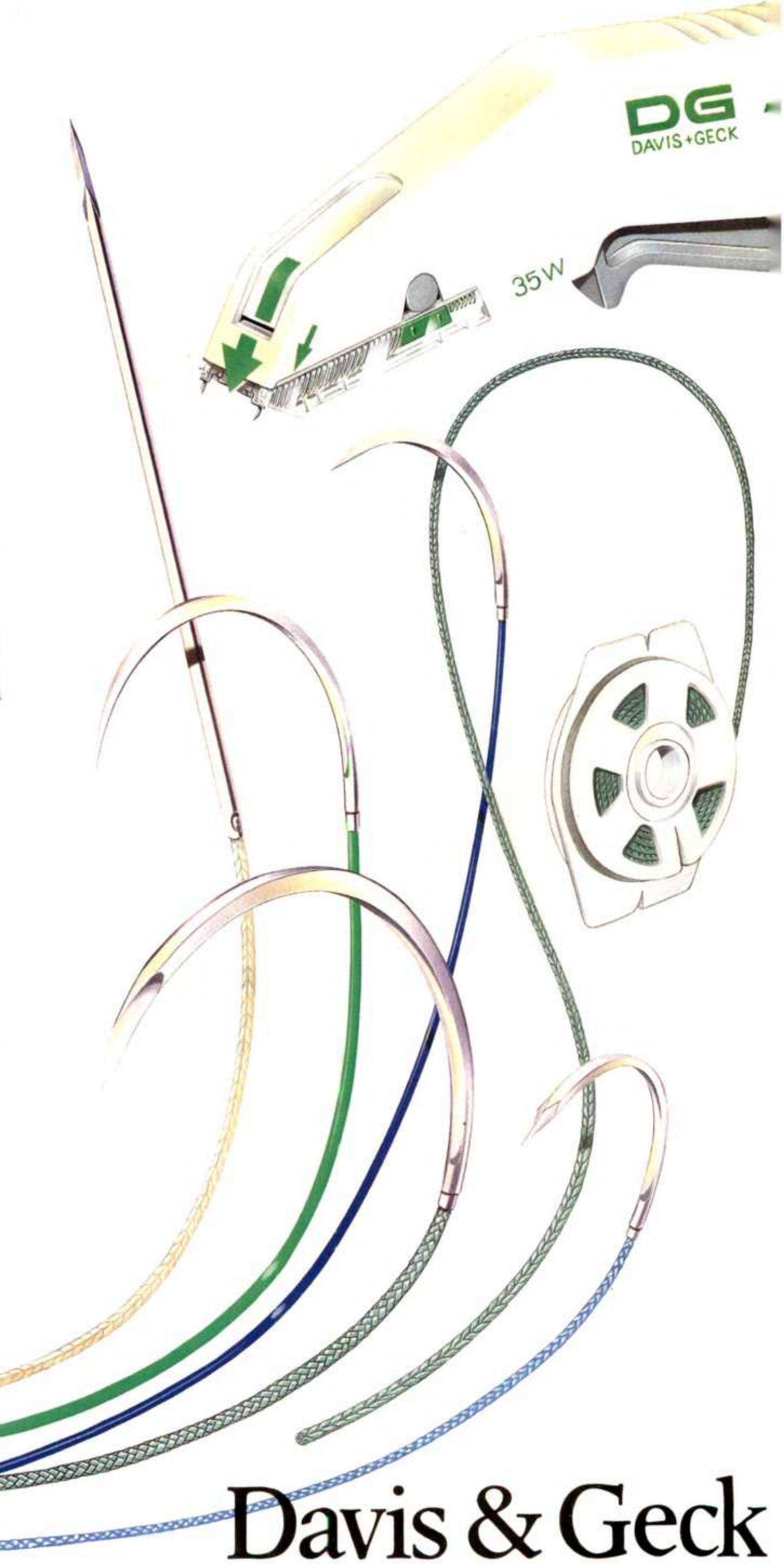

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Short note

Br. J. Surg. 1988, Vol 75, April, 317

Surgical glove perforations

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An intact barrier between the hands of a surgical team and the tissues of a patient undergoing operation is important if transmission of disease in either direction is to be prevented. It is widely assumed that surgical gloves provide such a barrier.

In this study we have determined the incidence of glove perforations in general surgical procedures, and tried to identify manoeuvres associated with an increased likelihood of perforation.

Methods

The gloves (Regent Dispo, LRC Products Ltd) used by all members of scrub teams performing general surgical procedures were collected over a 1-month period. Scrub team members completed a questionnaire at the end of each procedure to accompany their gloves. Questions specifically asked the nature of the operation, whether the team member was aware of puncturing a glove during the procedure and, if so, what manoeuvre was being performed at the time.

Gloves were tested for holes using a similar technique to that of Church and Sanderson[1] and McCue *et al.*[2]. Each glove was inflated with water and the cuff tied. Each finger and then the palm was individually squeezed and perforations were easily seen by the production of a fine spray of water. Pairs of gloves were classified as either perforated or not perforated.

The sensitivity of the test was evaluated in previously unused gloves perforated once with needles of various sizes. It proved 80 per cent effective in detecting holes made by 25 gauge needles (32/40 gloves) and 100 per cent effective in detecting holes made by 23 gauge needles (40/40 gloves). Controls using 30 pairs of unused gloves produced no detection of any perforations.

Gloves were divided into groups according to the user: surgeon, scrub nurse, first assistant or second assistant. They were then further divided into those which had been used in 'major' procedures and those which had been used in all other procedures. 'Major' procedures were those involving a one-layer abdominal wound closure with nylon on a cutting needle—the 'mass closure' technique.

Statistical analysis was performed using the χ^2 test.

Results

The overall perforation rate for all gloves tested was 127 pairs out of 339 (37·5 per cent). The results for each group are shown in *Tables 1–4*. Unfortunately, eight pairs of surgeon's gloves in the mass closure group were discarded before they could be collected for testing.

The overall perforation rates for surgeons' and scrub nurses' gloves were very similar (48·2 per cent and 42·5 per cent respectively). Both were significantly greater than the rate for first and second assistants' gloves combined (surgeons *versus* assistants, $P<0{\cdot}005$; scrub nurses *versus* assistants, $P<0{\cdot}02$). However, in the surgeons' group, perforations were more common in the mass closure group than in the other operations group (73·5 per cent compared with 28·6 per cent, $P<0{\cdot}01$), whereas scrub nurses' gloves did not show this difference; first assistants also showed this significant relationship ($P<0{\cdot}05$).

For surgeons, 21 of the 54 perforations were known (38·9 per cent) compared with 5 out of 51 (9·8 per cent) for scrub nurses and 8 out of 19 (42·1 per cent) for first assistants. There were no known perforations in second assistants' gloves.

The majority of known perforations occurred during mass wound closure.

Table 1 *Surgeons' gloves*

	No.	Perforated pairs	χ^2 test
Mass closure operations	49	36 (73·5%)	$P<0{\cdot}01$
Other operations	63	18 (28·6%)	
Total	112	54 (48·2%)	
Known perforations		21	

Table 2 *Scrub nurses' gloves*

	No.	Perforated pairs	χ^2 test
Mass closure operations	57	23 (40·4%)	$P=$ n.s.
Other operations	63	28 (44·4%)	
Total	120	51 (42·5%)	
Known perforations		5	

n.s., Not significant

Table 3 *First assistants' gloves*

	No.	Perforated pairs	χ^2 test
Mass closure operations	45	15 (33·3%)	$P<0{\cdot}05$
Other operations	44	4 (9·1%)	
Total	89	19 (21·3%)	
Known perforations		8	

Table 4 *Second assistants' gloves*

	No.	Perforated pairs	χ^2 test
Mass closure operations	14	2 (14·3%)	$P=$ n.s.
Other operations	4	1 (25%)	
Total	18	3 (16·7%)	
Known perforations		0	

n.s., Not significant

Discussion

Church and Sanderson reported a glove perforation rate of 11·5 per cent in 130 gloves from unspecified surgical cases[1]. In our study, the overall perforation rate (37·5 per cent) is more than three times higher in a much larger sample. This difference is possibly related to our analysis in terms of pairs of gloves and not individual gloves, and also to limiting our study to general surgical operations. We regard our figure as a probable underestimate because the sensitivity of our test was 80 per cent in detecting smaller (25 gauge) holes, and all scrub team members were aware of the study, thus possibly being more careful in their technique.

Major operations involving use of the mass closure technique carry a high risk of glove puncture for the operating surgeon: 12 out of 21 known perforations occurred during this manoeuvre and, of all glove perforations in the surgeons' group, a significantly higher number occurred in the mass closure group ($P<0{\cdot}01$), suggesting that the unknown perforations were also associated with this manoeuvre. Perforations in the scrub nurses' group appear to be related to the handling of instruments and needles, irrespective of the procedure being carried out.

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Br. J. Surg. 1988, Vol 75, April, 318–320

Comparison of colonic reservoir and straight colo-anal reconstruction after rectal excision

The clinical and physiological results in 13 patients having a colonic J reservoir–anal anastomosis (CR) and 15 consecutive patients having a straight colo-anal reconstruction (SC) have been compared. The groups were matched for age, sex, level of tumour and proximal and distal resection margins. The incidence of postoperative complications was similar in each group. The mean follow-up in CR patients was 7 ± 4 *months and* 47 ± 23 *months in SC patients. Stool frequency per 24 h was* ≤ 2 *in all CR patients while it was* >2 *in 40 per cent of the SC patients* ($P<0{\cdot}05$)*. Three CR patients and six SC patients had minor incontinence, all but one of the rest were fully continent. One patient had a major leak. There was no significant difference in mean resting anal voluntary contraction pressure in the two groups, with mean values within the normal range. The mean rectal sensitivity threshold volume in CR patients* (83 ± 30 *ml) and SC patients* (52 ± 22 *ml) was significantly different* ($P<0{\cdot}05$) *as was the mean maximum tolerable volume* (317 ± 122 *ml and* 174 ± 83 *ml respectively,* $P<0{\cdot}01$)*. There was no significant difference in balloon expulsion testing, defaecating proctography or methyl cellulose evacuation in the two groups. The addition of a colonic reservoir appears to avoid the high stool frequency occurring in some patients after straight colo-anal anastomosis.*

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Keywords: Colo-anal anastomosis, colonic reservoir/pouch, rectal cancer

Anterior resection of tumours of the middle third of the rectum appears to yield long-term survival rates and local recurrence rates similar to those following total rectal excision[1–5]. Despite the introduction of the circular stapling gun, restorative anastomoses for tumours low within the pelvis, especially in male patients, can be technically difficult.

In 1972, Parks described an endo-anal technique for colo-anal anastomosis[6]. This procedure has since been widely used not only for malignant and benign tumours of the rectum, but also for rectovaginal fistula[7], haemangioma[8] and radiation proctitis[9,10]. However, patients often experience urgency and increased frequency of bowel movements after this procedure and postoperative functional results have been variable[11]. This is most likely to be due to the lack of reservoir function in the colonic 'neorectum' in some patients.

Lazorthes *et al.*[12] have described the incorporation of a colonic double loop reservoir anastomosed directly to the anal canal. This is carried out via a posterior trans-sphincteric approach[12], but colo-anal anastomosis carried out endo-anally avoids division of the anal sphincters. Furthermore, only by using a similar anastomotic technique is it possible to determine the effectiveness or not of a reservoir in the reconstruction. Accordingly, a reservoir–anal canal anastomotic technique via an endo-anal approach was employed in a series of patients and the clinical results and physiological outcome compared with an unselected group of patients who had had a colo-anal anastomosis by the same technique but without a reservoir.

Patients and methods

Thirteen patients who underwent rectal excision with colonic reservoir and colo-anal anastomosis between March 1985 and February 1986, and fifteen consecutive patients who underwent rectal excision and straight colo-anal anastomosis between August 1979 and March 1986 were studied. All 13 patients in the reservoir group and 9 in the straight group were operated on by the senior author. The other six patients in the straight group were operated on by three of the senior surgeons at St. Mark's Hospital. Basic details of the patients are shown in *Table 1*. Most had had a proximal defunctioning stoma, including a loop colostomy in 10 patients and a loop ileostomy in 1 patient in the straight colo-anal group, and 5 reservoir patients had a loop colostomy and 8 a loop ileostomy. The stoma had been closed in all cases.

Student's *t* test, Wilcoxon's rank paired test and Fisher's exact test were used in the analysis of data.

Operative technique

In all but three patients the colo-anal anastomosis was carried out by the technique described by Parks and his colleagues[8]. Minor modifications included the use of 2/0 polyglactin suture material and a suction drain placed in the pelvic cavity via an abdominal stab incision. Three patients in the straight colo-anal group, all with carcinoma of the mid-rectum, had a colo-anal anastomosis using the EEA® (Autosuture Co., UK) stapling gun. The lower purse-string suture was inserted per abdomen at the anorectal junction. The lower 'doughnut' ensured that the anastomosis was to the anal canal.

The colonic reservoir was constructed from two loops of terminal proximal colon 10 cm in length using two layers of continuous polyglactin sutures 2/0. The anterior layer of the reservoir was sutured to a point distally which left a defect wide enough to admit two fingers. This was then joined to the anal canal in the conventional endo-anal fashion. The splenic flexure was well mobilized in all cases.

Intravenous antibiotics (gentamicin and metronidazole) were given

Table 1 *Basic clinical and pathological details in patients with and without a colonic reservoir*

	With	Without
Number of patients	13	15
M/F	8/5	13/2
Age (years)	58 ± 13 (40–79)	63 ± 14 (29–84)
Carcinoma	8	13
Villous adenoma	4	1
Rectovaginal fistula (trauma)	—	1
Cavernous haemangioma	1	—

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Table 2 *Complications with and without a colonic reservoir*

	With	Without
Number of patients	13	15
No complications	5	7
Anastomotic dehiscence	2	4
Obstruction (laparotomy)	3	0
DVT/PE	1	2
Wound	3	3
Stricture (dilatation)	1	1

DVT, deep vein thrombosis; PE, pulmonary embolism

Table 3 *Function after closure of the temporary stoma with and without a colonic reservoir*

	With	Without
Number of patients	13	15
Stool frequency/24 h	1·4 (0·5–2)	2·3 (1–6·5)
Consistency		
Formed	13	11
Porridge	—	4
Medication	1 (+1 using suppositories)	3
Continence		
Normal	10	9
Minor leak	3	6
Major leak	0	1
Urgency	1	1
Perianal irritation	1	0
Flatus/faeces differentiation	10	10

with induction of anaesthesia and for three doses postoperatively. Anastomotic integrity was confirmed by a water soluble contrast enema before closure of the proximal defunctioning stoma. An anastomotic leak was defined as any palpable defect in the anastomosis and/or any pelvic sepsis.

Functional assessment

All 28 patients were assessed clinically and 19 underwent physiological assessment. Nine of these had had straight and ten a reservoir reconstruction. Frequency of defaecation per 24 h, stool consistency, and continence whether normal, minor disturbance (smear or mucous leak requiring a pad) or major disturbance (faecal incontinence) were determined. The presence of urgency, perianal irritation and the ability to differentiate between flatus and faeces were also assessed.

Anal manometry was carried out using a closed water-filled microballoon connected via a stiff polyethylene tube to a transducer and pressure recorder. Resting and maximum voluntary squeeze pressures were measured and the rectosphincteric reflex tested[13]. A latex balloon inserted per anum into the reservoir was inflated with water in increments of 20 ml to determine the threshold of rectal sensation. The maximum tolerable volume was then measured by continuing the inflation until intolerable discomfort was produced[14]. The balloon contained a pressure probe within it which recorded pressure at each volume increment. This enabled the compliance of the reservoir to be estimated. Compliance was given by change in pressure per unit volume (P/V)[14].

Transit studies were performed using intestinal radio-opaque markers as described by Hinton[15]. Emptying of the neorectum was assessed by three methods: balloon expulsion, videoproctography and methyl cellulose recovery. The patient, lying in the left lateral position, was asked to expel a latex balloon containing 50 ml of water placed into the neorectum[16]. Barium (120 ml) was instilled per anum and the patient screened while sitting on a radiolucent commode. The time to expulsion of barium on straining was then recorded by videocinematography[17]. Methyl cellulose (250 g) was placed in the reservoir and the patient asked to defaecate. The amount recovered was measured and expressed as a percentage of the total instilled.

Results

The site of the lesion within the rectum, the mean pre-operative sigmoidoscopic distance from the anal verge to its lower edge and the mean diameter of the carcinomas were similar in the two groups. In the majority, the lesion was in the mid or lower rectum. In one patient in the reservoir group a tubulovillous adenoma extended to within 2 cm of the anal verge. The Dukes' classification and the histological grade of the carcinomas removed were also similar in the two groups. The mean length of the distal margin of resection was 2·6 ± 1·3 cm (± s.d.) in patients without and 2·6 ± 1·7 cm in those with a reservoir. In no patient with carcinoma was the distal resection margin <2 cm.

Complications are shown in *Table 2*. There were no operative deaths. Some degree of breakdown of the colo-anal anastomosis occurred in four patients without and two with a reservoir. In all cases healing took place by secondary intention leaving one patient with a stricture in each group. This was treated by one dilatation under anaesthetic in each case.

The mean total hospital stay both for the primary operation and closure of the stoma was 28 ± 10 days for those with a reservoir and 31 ± 10 days for those without and the stoma was closed after the primary operation at a mean interval of 2·7 ± 1·7 months and 2·5 ± 0·6 months respectively.

The mean (± s.d.) interval between closure of the stoma and the present assessment was 47 ± 23 months (range 5–78 months) in patients without, and 7 ± 4 months (range 3–15 months) in those with a reservoir. The respective mean stool frequencies of 2·3/24 h and 1·4/24 h were not significantly different (*Table 3*). However, the variance of frequency was significantly less in the reservoir group ($P<0{\cdot}05$). Thus 40 per cent of those without a reservoir had a stool frequency of > 2/day whereas in all patients with a reservoir frequency was ≤ 2/24 h (*Figure 1*). There was no significant difference in continence, urgency, or the ability to differentiate between flatus and faeces. No patient had major faecal leakage.

There was no significant difference in mean anal resting or voluntary contraction pressure between the two groups, with values within the normal range (*Table 4*).

There was no significant difference in evacuation function between the two groups: however, three patients with a reservoir were unable to evacuate fully on proctography.

There was no significant difference between the two groups in the compliance of the neorectum.

Discussion

Endo-anal colo-anal anastomosis is a well-established technique and has been applied in various diseases[7–11]. If the procedure is justified on pathological grounds the next consideration must be the quality of life. In practice this means function and there is already evidence that the addition of a colonic reservoir may improve this aspect[12,18]. However, to date there has been no comparison of function between patients with a colonic reservoir construction and those without but using the same anastomotic technique.

In the present series, continence rates were similar in the two groups but frequency of defaecation after reservoir construction

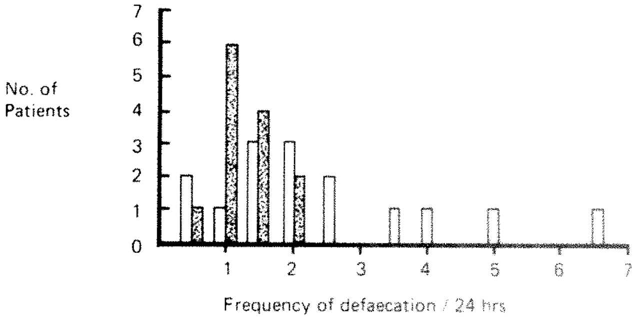

Figure 1 *Frequency of defaecation per 24 h in patients having reservoir* (▨) *and straight colo-anal* (☐) *reconstructions*

Table 4 *Physiological variables in the two groups with and without a colonic reservoir*

	With	Without
Number assessed	10	9
Anal pressure (cmH_2O)		
Rest	68 ± 14	71 ± 21
Voluntary contraction	111 ± 33	99 ± 38
Rectoanal reflex +ve	3	6
Rectal sensitivity threshold (ml)	83 ± 30*	52 ± 22
Maximum tolerated volume (ml)	317 ± 122†	174 ± 83
Balloon expulsion +ve	9	8
Methyl cellulose evacuation % (range)	65 (35–96)	62 (21–95)
Evacuation complete on proctography	6/9	7/8
Transit normal	6/7	6/7

Values are means ± s.d. Significant difference between groups with and without colonic reservoir: * $P<0.05$, † $P<0.01$

was associated with a significantly smaller variance. Frequency is known to improve in the first year after low colorectal or colo-anal anastomosis[19] but it remains high in a proportion of patients[11]. This was observed in the present study with 40 per cent of the patients having a stool frequency of more than twice per 24 h after straight colo-anal reconstruction. Only one of these patients had been followed for under 12 months, the interval from operation to this assessment being three or more years for the rest. In contrast, none of the patients in the reservoir group had a stool frequency of more than twice per 24 h despite a mean follow-up of only 7 months, and the mean stool frequency per 24 h in the reservoir group of 1·4 might be expected to decrease with the passage of time. This frequency is very similar to that reported by Parc *et al.*[18] of 1·1 per 24 h at only 3 months postoperatively.

The patients undergoing straight colo-anal reconstruction were operated on by four different surgeons. Accepting that this may introduce another factor when comparing this group of patients with the reservoir group, it is also relevant that these surgeons were all very experienced in the straight colo-anal reconstruction. Equally, it would be fair to say that the 13 patients in the reservoir group represent the first 13 patients undergoing this form of reconstruction performed by the senior author and that this may, accepting a learning process, have adversely influenced the overall results for this group. However, the technique for colonic pouch–anal anastomosis is identical to that of ileal pouch–anal anastomosis with which the surgeon has been familiar.

The physiological assessment in the present study suggests that this benefit in stool frequency may be due to the greater capacitance afforded by the reservoir compared with the straight reconstruction. This is in line with the finding of Lazorthes *et al.*[12] of an inverse relationship between frequency of defaecation and maximum tolerable volume for colonic reservoirs; a similar observation has been made in ileo-anal reservoir patients[14]. The findings suggest that the use of a reservoir reduces the chance of frequency of defaecation occurring and that this is probably due to increased capacitance. It should thus offer the patient a more predictable function postoperatively. This is an important consideration when treating cancer in which, despite an apparently curative operation, the prognosis of some patients will be short.

The use of a reservoir may, however, lead to difficulty in evacuation. Three patients in the study had incomplete evacuation on videoproctography and although function was clinically normal in two, the third needed suppositories to evacuate fully. This may be related to the significantly greater rectal sensitivity threshold volume observed in the reservoir group. We would aim to study the reservoir group again in a few years time to undertake an assessment of whether or not there has been any change in function or increase in size of the reservoir.

The manometric studies support the finding of Lane and Parks that the recto-anal inhibition reflex can persist after excision of the rectum and colo-anal reconstruction[20]. Lane and Parks observed that the reflex was often absent in the early postoperative period and it is possible therefore that the number with a positive reflex in the reservoir group may increase with time.

In summary, compared with a straight colo-anal reconstruction the addition of a colonic reservoir has resulted in a significant increase in rectal sensitivity volume and capacitance. There is less variance in stool frequency with all patients with a reservoir having a 24 h stool frequency ≤ 2 at only a mean of 7 months postoperatively. The results support the concept that the increased capacity of the neorectum is an advantage for patients undergoing colo-anal reconstruction.

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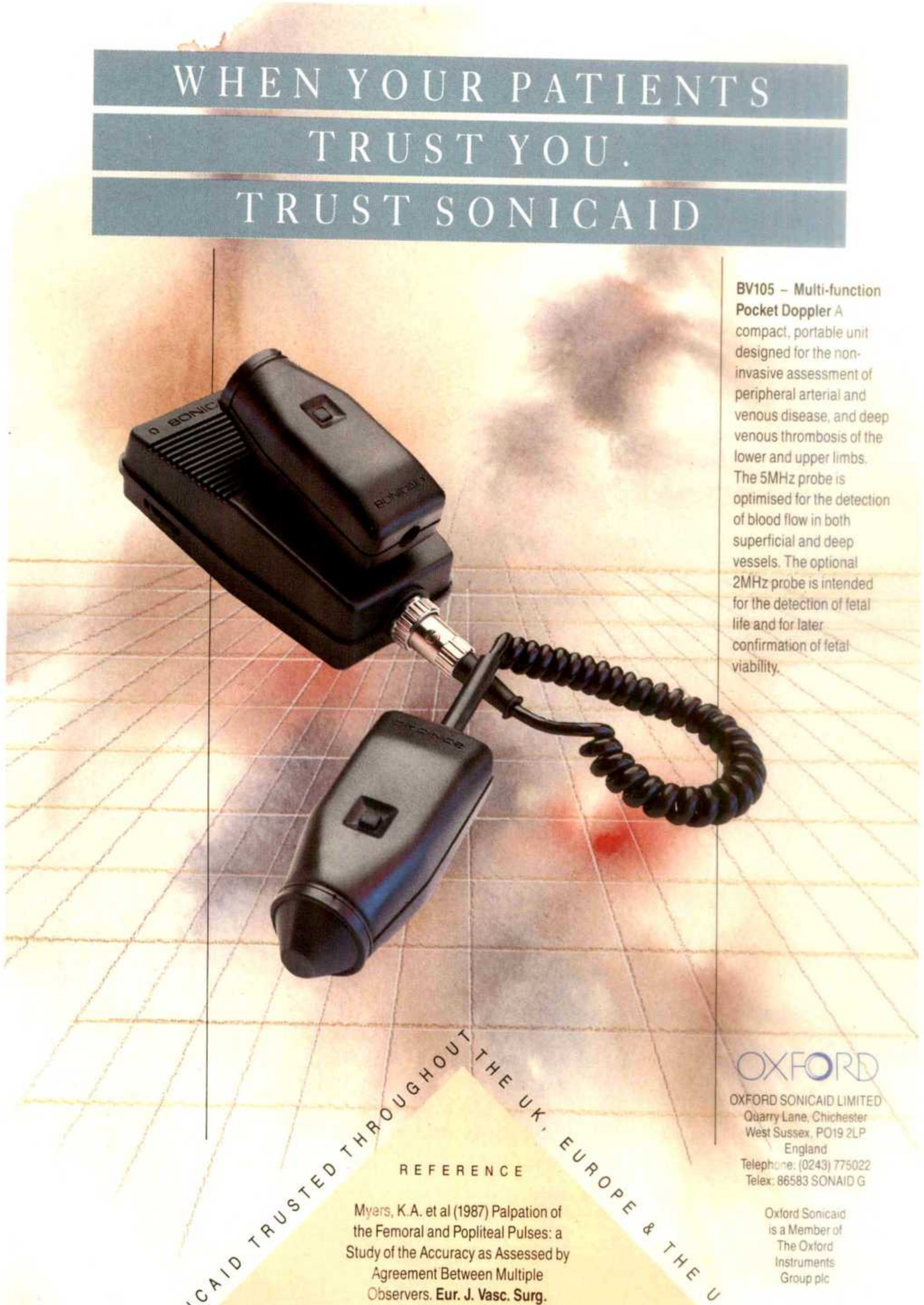

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Proceedings of the St Mark's Hospital 150th Anniversary International Conference

Edited by **R C G Russell** MS, FRCS and **J P S Thomson** MS, FRCS

The conference "Frontiers in Colorectal Disease" held at the Barbican Conference Centre in May, marked the 150th anniversary of St Mark's Hospital for Diseases of the Rectum and Colon. With 1295 delegates from 45 different countries this was one of the largest gatherings ever of those who practise in the growing specialty of coloproctology.

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Clinical and functional results after restorative proctocolectomy

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Of 84 patients who underwent restorative proctocolectomy with an ileoanal reservoir in 21 Italian departments of surgery, 51 had ulcerative colitis, 32 familial polyposis and 1 intractable constipation. Follow-up information is available for all 58 patients who had their ileostomy closed, the length of follow-up ranging between 2 and 78 months. There were no operative deaths. A failure rate (i.e. excision of the pouch) of 3 per cent was observed. Sepsis was the most common postoperative complication, and was most often related to ileoanal anastomosis dehiscence (15 per cent), followed by small-bowel obstruction requiring laparotomy (10 per cent). Clinical 'pouchitis' occurred in 14 per cent of patients after ileostomy closure. The average frequency of defaecation was four motions per 24 h; evacuation was spontaneous in all patients and only 5 per cent complained of troublesome faecal soiling while 34 per cent had occasional incontinence to flatus and mucus. Patients with a short or absent rectal cuff had a lower rate of incontinence (30 versus 48 per cent, difference not statistically significant) without any increase in the frequency of genito-urinary disorders. None of the two most used reservoirs, the J (n = 40) and S pouch (n = 17) showed significant superiority in terms of bowel frequency and continence. Incontinence was more likely in patients whose ileostomy closure had been delayed for more than one year.

Keywords: Proctocolectomy, ileoanal anastomosis, ileal pouch

Restorative proctocolectomy with construction of an ileoanal reservoir has been used in the past 10 years for the radical treatment of ulcerative colitis and familial polyposis. The aims of this procedure are to excise all the diseased large bowel and to avoid a permanent stoma. Since the first report in 1978[1], the operation has become widely used in Northern Europe, Japan and the United States[2–4]. In Italy it was first performed in 1980 (*Table 1*), the delay reflecting the popularity of colectomy and ileorectal anastomosis as well as the problems related to self-catheterization[5]. The present paper repeats the results of a multicentre study of 84 patients operated on in 21 hospitals in Italy during the last 6 years. Most reports in the literature are based on the experience derived from specialist colorectal units and controversy still exists[6–8]. Our aim was to study the outcome when a relatively new and complex operation was carried out in departments of general surgery and to assess whether the type of reservoir and length of the rectal cuff affected postoperative function.

Patients and methods

Patients

Eighty-four patients underwent restorative proctocolectomy with an ileoanal reservoir between March 1980 and August 1986 in the twenty-one departments of surgery taking part in the Italian Registry. Of these 84 patients, 51 had chronic ulcerative colitis, 32 familial polyposis and 1 intractable constipation. There were 51 men and 33 women aged 16–64 years (median 37 years). Of the 84 patients, 28 had a previous colectomy with ileostomy without excision of the rectum, whereas 56 underwent one-stage colectomy and pouch construction. In all patients, clinical, radiological and histological findings were carefully reviewed before surgery to establish the correct diagnosis and exclude cancer and Crohn's disease.

Selection criteria for the pouch operation included a severely diseased rectum (i.e with strictures, dysplasia or 'carpet' polyposis), a strong desire to avoid a permanent stoma and adequate anal sphincter function as assessed by digital examination or anorectal manometry

Operation

Thirty-two patients (38 per cent) were on corticosteroid treatment at the time of the pouch operation. The surgical procedure has been described in detail by others[3–5]. A J pouch was carried out in 53 cases (63 per cent), a three-loop reservoir with an efferent limb 3–4 cm long in 29, and an L or W pouch in 2. A GIA stapler was used in 12 patients with a two-loop reservoir. Close dissection of the rectum was performed A long rectal cuff (over 6 cm) was left in 27 cases (32 per cent); in 52 patients (62 per cent) the cuff was shorter. In five patients the rectum was completely removed to reduce the extent of mucosectomy and decrease the risk of pelvic abscess formation, bleeding and damage to the internal sphincter. The mucosa was removed from the rectal stump down to the dentate line via a peranal approach The pelvis was always drained by a tube placed either through the perineum along the intersphincteric plane or through the abdominal wall.

In all but two patients a temporary diverting loop ileostomy was carried out.

Analysis of records and follow-up

All the clinical data were recorded on Registry forms similar to those used in a previous study[6] Clinical information was available on all of the

Table 1 *Complications following the reservoir operation in 84 patients*

Complications	Number of patients	Percentage of patients
Mortality	0	0
No complications	54	64
Pelvic sepsis with ileoanal anastomosis defect (1 failure with permanent ileostomy)	13	15
Small-bowel obstruction requiring laparotomy	8	10
Reservoir anastomotic defect	3	4
Reservoir necrosis requiring reintervention	3	4
Anastomotic narrowing requiring dilatation	2	2

The work was carried out through the cooperation of the Italian Registry.

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Table 2 *Complications following closure of the ileostomy in 58 patients*

Complications	Number of patients	Percentage of patients
Clinical 'pouchitis'	8	14
Small-bowel obstruction requiring medical treatment ($n=3$) or laparotomy ($n=1$)	4	7
Anastomotic dehiscence requiring reintervention	2	3
Anastomotic stricture requiring reintervention	1	2

Table 3 *Function in 58 patients assessed at 2–78 months (mean 14 months) after closure of the ileostomy*

Function	Number of patients	Percentage of patients
≤4 motions/24 h	35	60
>4 motions/24 h	24	41
Spontaneous evacuation	58	100
Antidiarrhoeal medication	19	33
Continence normal	35	60
Minimal leak (flatus and mucus)	20	34
Troublesome leak (faeces)	3	5
Altered sexual function (disordered ejaculation)	3	5

58 patients who had their ileostomy closed. The average time of follow-up from the closure of the ileostomy was 14 months (range 2–78 months). The χ^2 test was used in the statistical analysis of the data.

Results

Complications

There were no operative deaths. Three patients (4 per cent) required permanent ileostomy: the first had postoperative necrosis of the reservoir, the second had faecal incontinence and persistent painful diarrhoea, and the third developed severe pelvic sepsis related to ileoanal anastomotic breakdown. Pelvic sepsis occurred in 12 other patients, all of whom had some defect in the ileoanal anastomosis (*Table 1*).

The anastomotic dehiscence healed either spontaneously or after surgical drainage in all but the above-mentioned patient. Two patients developed anastomotic narrowing which required dilatation. Minor separation of the reservoir sutures were observed in three patients: none required reintervention and all healed after delayed closure of the loop ileostomy. Ten (31 per cent) of the 32 patients who were on steroids at the time of the pouch operation developed anastomotic breakdown, compared with 7 (14 per cent) of the remaining 52, but the difference was not statistically significant. Eight patients developed small-bowel obstruction requiring laparotomy after surgery, but in no case was the pouch involved in the obstruction. Severe ischaemia of the reservoir leading to complete necrosis and the need for relaparotomy occurred in three patients: a new pouch was constructed in two of them, whereas one patient (mentioned above) had a permanent ileostomy.

Small-bowel obstruction was the commonest complication after closure of the ileostomy, occurring in four patients, followed by ileal suture line dehiscence and stricture. Eight patients (14 per cent) had at least one episode of non-specific reservoir ileitis (pouchitis) with fever, diarrhoea and discharge of pus which abated after therapy with metronidazole and steroid irrigation (*Table 2*). Bacterial overgrowth was observed in one of these eight cases. The complication rate after either the pouch operation or ileostomy closure was 55 per cent. Of the overall complications, 60 per cent occurred in patients operated upon for colitis, and 40 per cent occurred in those who underwent surgery for polyposis, but the difference was not statistically significant.

Of the 53 patients with a two-loop reservoir, 15 (28 per cent) had postoperative complications, compared with 12 (41 per cent) of the 29 cases with an S pouch; again the difference was not statistically significant.

Function

Fifty-eight patients had their ileostomy closed for at least 2 months and were eligible for functional evaluation (*Table 3*). All patients were capable of defaecating spontaneously, and none required catheterization of the pouch. Frequency of defaecation varied between one and ten motions per 24 h. The pouch had to be emptied four times or less in 35 patients (60 per cent).

Fifteen patients had six or more daily bowel motions (*Figure 1*). No significant correlation was found between the type of reservoir and the frequency of defaecation (*Table 4*). High bowel frequency required antidiarrhoeal medication (usually loperamide) in 34 per cent of patients.

Continence

Continence was normal in 35 patients; 20 had some disturbance and wore a pad at least part of the time; a troublesome leak was present in 3 cases. One of them improved with biofeedback, and in this case anorectal manometry indicated that the internal sphincter was mainly affected. After surgery, the anal canal in this patient was shortened by 4 cm to 3 cm, resting tone decreased from 150 to 30 mmHg and both mucus and faecal leaks occurred after ileostomy closure. Moreover, owing to perineal discomfort and ileal spasms related to the desire to defaecate, the patient could not effectively contract his external sphincter and therefore developed soiling. After a course of sphincter exercises, associated with endoluminal balloon distension, resting tone increased to 59 mmHg and voluntary contraction from 100 to 250 mmHg.

As shown in *Table 4*, no correlation was found between the type of reservoir and defects in anal continence. A higher incidence of soiling occurred in those patients in whom the

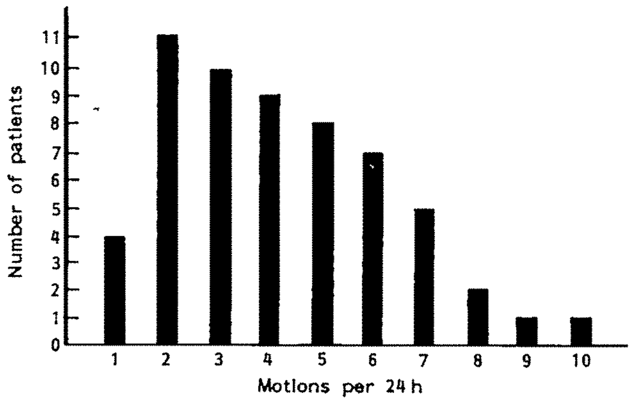

Figure 1 *Frequency of defaecation per 24 h in 58 patients following closure of the ileostomy*

Table 4 *Type of reservoir and postoperative function in 57 patients*

	Patients with:			
	Two-loop reservoir		Three-loop reservoir	
Function	Number	(%)	Number	(%)
High bowel frequency (4 motions/24 h)	13/40	(32)	5/17	(29) n.s
Disordered continence	13/40	(32)	9/17	(53) n s.

rectal cuff had been left longer than 6 cm at operation (*Table 5*). We observed six cases of incontinence in the twelve patients whose ileostomy closure had been delayed for more than 1 year, and fifteen cases in the forty-three patients who had their stoma closed in less than 12 months. This difference was not statistically significant. Three patients had minor postoperative sexual disorders, mainly retrograde ejaculation. The length of the rectal cuff did not correlate significantly with disordered sexual function (*Table 5*).

Discussion

According to some, restorative proctocolectomy and ileoanal reservoir is the operation of choice in the treatment of ulcerative colitis and familial polyposis. However, some problems still need to be solved, such as pelvic sepsis, 'pouchitis', high bowel frequency and anal continence disorders—problems that are especially common in operations performed during the 'learning' phase of the procedure[5]. The operative mortality is negligible, mainly because the patients are young and the operation is carried out by experienced surgeons specializing in colorectal surgery[8–11] (*Table 6*). As it cannot be performed in malnourished subjects or under emergency conditions, a first-stage colectomy may be required in ulcerative colitis. Moreover, because of the current use of a diverting stoma, a three-stage procedure was needed in one-third of our patients.

The pre-operative use of systemic steroids did not increase the risk of suture dehiscence in this study although different conclusions were reached in a previous study[6]. The failure rate of the procedure, that is the need for excision of the pouch and permanent ileostomy, was 4 per cent in our experience. This is in keeping with a rate of loss of 5 per cent or less, as reported in all but two studies in the recent literature (*Table 6*). The incidence of pelvic sepsis, usually the result of ileoanal anastomosis breakdown, ranges from 8 per cent to 22 per cent in the literature, being 15 per cent in our series. Pelvic sepsis is more common in patients with a long rectal cuff who require a wider mucosectomy with bleeding and subsequent haematoma formation[13]. To decrease the risk of pelvic sepsis, it is advisable to perform a temporary diverting stoma[11]. One of our three failures was due to severe pelvic sepsis following ileoanal suture line dehiscence in a patient who did not have such a diverting stoma. However, loop ileostomy may be followed by small-bowel obstruction requiring laparotomy[9–10] and loop ileostomy can perhaps be avoided in selected cases treated by experienced surgeons[14].

Table 5 *Length of the rectal cuff in relation to postoperative function*

	Patients with:			
	Short cuff (<6 cm)		Long cuff (>6 cm)	
Function	Number	(%)	Number	(%)
Disordered continence	10/33	(30)	12/25	(48) n.s
Sexual disorders	2/57	(4)	1/27	(4) n s.

The type of reservoir (two- or three-loop) did not significantly influence the incidence of postoperative complications in this Italian experience. Others[9] advocate the four-loop pouch, whereas the lateral, J and S produced a similar complication rate in one reported series[12]. Ischaemia leading to necrosis of the ileal reservoir required reconstruction of the pouch in two of our patients and excision in one. To prevent this complication the pouch should reach the dentate line and have an adequate blood supply, the critical factor being the length of the superior mesenteric artery. The S pouch generally reaches 2–4 cm more caudal than the J pouch which can be lengthened by cutting the branch vessels and sparing the marginal arcade[15].

The aim of the operation is to eradicate the disease and preserve good function. High bowel frequency, faecal incontinence and perineal discomfort due to ileal spasms and weak sphincters were resolved by biofeedback in one of our patients. Small-bowel myotomy has also been suggested as a means of decreasing intestinal contractions and fibrosis[16]. The average number of evacuations varies between three and seven in 24 h and is higher in the short-term follow-up of patients who had a J pouch for colitis[6–11]; it is lower in patients operated on for polyposis and those with good emptying rates and high capacity[9]. A significant correlation between pouch design and bowel frequency was not found in our study, possibly because of the short follow-up, whereas others have reported a lower frequency 12 months after construction of triplicated pouches[12]. Inflammation in the reservoir was found in 90 per cent of patients on histological examination, but in most cases this was subclinical[9]. Pouchitis associated with bacterial overgrowth is not an uncommon finding[11]: it presents with faecal frequency, loose stools and general weakness, and may require a loop ileostomy if there is no response to conservative treatment[7]. The number of colonies were found to increase in the reservoir 2–3 years after the operation in a group of 36 patients operated on at St. Mark's Hospital and evaluated by the first author of this paper (M. Pescatori, unpublished data). Others have found that the faecal flora of the pouches shows a greater predominance of anaerobes and increased numbers of *Bacteroides* when compared with the faecal flora of ileostomies, without any correlation with bowel function[12]. More than one-third of the patients need medical therapy following pouch construction, usually antidiarrhoeal agents, steroids or antibiotics[11], mainly because they tend to have high bowel frequency or soiling.

Self catheterization was needed to empty the S reservoir in the early experience at St. Mark's Hospital[5], but shortening of the afferent limb allowed spontaneous evacuation[17]. All of our

Table 6 *Clinical and functional results following restorative proctocolectomy and ileoanal reservoir as reported in the recent literature*

		Diagnosis										Incontinence	
Author	*n*	UC	FP	O	Reservoir (majority)	OM (%)	Failure (%)	Pelvic sepsis (%)	Pouchitis (%)	Defaecation 24 h	SE (%)	Major	Minor
Fonkalsrud[8]	49*	44	5		L	0	5	11	44	6	100	0	7
Nicholls *et al.*[9]	119	98	20	1	J.S.W.	1	10	19	11	4	76	3	18
Dozois[10]	369	336	33		J	0	5	11	7	7	100	5	47
Utsunomiya[11]	55	17	38		J	NR	11	22	10	5	100	2	20
Goldberg and Rothenberger[11]	91	85	5	1	S	0	5	10	34	6	92	4	39
Cohen[11]	125	119	6		J.S.	0	2	8	NR	6	97	5	4
Nasmyth *et al.*[12]	39	34	5		J.S.L	0	5	18	NR	6	98	0	61
Hulten[11]	36	34	1	1	J.S	0	0	8	NR	4	100	0	NR
Italian Registry	84	51	32	1	J.S.	0	3	15	11	4	100	5	34

UC, ulcerative colitis; FP, familial polyposis; O, other L, lateral; J, S, W, two-, three-, four-loop; OM, operative mortality; SE, spontaneous evacuations, NR, not reported; * children patients with a three-loop reservoir are capable of defaecating without a catheter. Minor defects in anal continence are not uncommon after restorative proctocolectomy, ranging in incidence from 7 per cent to 47 per cent in various series[11]. Only 5 per cent of our patients suffered from troublesome faecal soiling and needed to wear a pad at all times. Sphincter exercise may be helpful in preventing incontinence following delayed ileostomy closure, but the striated sphincters usually remain effective in these young patients. An early temporary postoperative decrease in resting tone has been recorded in the anal canal, followed by a progressive restoration of normal values in 86 per cent of patients[18]. A deficiency of the internal sphincter is therefore the main cause of leakage and should be prevented by careful selection of the patients on the basis of anal manometry, and by avoiding the use of anal dilators. Damage to the sphincter may also be related to extensive mucosectomy. In this study incontinence was more likely to occur in patients with a long rectal cuff (48 per cent of the cases) although these differences were not statistically significant. Postoperative incontinence is more likely in patients over 55 years of age[10]. Genital and urinary function are not affected in the majority of patients, as pelvic dissection is kept close to the rectal wall and the negligible incidence of sexual disorders reported mainly concerns patients over 50 years of age[11]. Increased damage of the pelvic nerves was not noted in the group of patients with a short rectal cuff in the study reported here.

In conclusion, the results of the Italian Registry show an acceptable incidence of postoperative complications, a low failure rate and satisfactory bowel function after restorative proctocolectomy and ileoanal reservoir. However, the risk of pouchitis and continence disorders necessitates careful selection of the patients. In subjects with a good rectum, psychological lability, sphincter defects, increasing age and the suspicion of Crohn's disease, proctocolectomy with ileostomy or a colectomy with ileorectal anastomosis are still indicated. There was no clear-cut difference between the two most-used reservoirs, the J and S, in our experience. Patients with a short cuff or no rectal cuff had slightly better sphincter function, without any increased incidence of genito-urinary disorders. The relatively high number of postoperative complications and anal continence disorders may be explained by the fact that none of the participating surgeons had performed more than 10 restorative proctocolectomies. Thus, the operation should be performed in a few specialized centres able to carry out accurate pre-operative assessment, correct surgical technique and appropriate postoperative management.

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Influence of proximal colostomy on the healing of a left colon anastomosis: an experimental study in the rat

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The healing of an experimental left colon anastomosis protected by a proximal diverting colostomy was studied in the rat. Collagen synthesis in the anastomotic area was measured by incorporation of [^3H]*proline. With a defunctioning proximal colostomy, the synthesis and accumulation of collagen in the anastomosis was diminished, and the anastomotic strength development delayed and reduced. The development of anastomotic strength seems to proceed according to the level of strain from intraluminal bulk. As the healing of the anastomosis protected by a diverting colostomy was uncomplicated, these findings should not contra-indicate the use of diverting colostomy.*

Keywords: Colonic anastomosis, colostomy, healing, collagen, collagen synthesis

Anastomotic complications after resection of the colon and rectum are frequent[1–3] and pose a serious threat to the recovery of the patient. A proximal colostomy is often used in order to divert the faecal stream and decompress the left colon in the treatment of colonic obstruction or the difficult colorectal anastomosis. Despite this protective measure, anastomotic complications do occur, but with lower morbidity[4–7].

The early healing pattern of experimental left colon anastomosis has been found to be modified by proximal colostomy for 7 days, with marked reduction of postoperative collagen accumulation in the colonic wall[8]. With proximal colostomy, the accumulation of collagen is limited to the vicinity of the anastomosis, in contrast to widespread collagen changes in the bowel wall found after anastomosis without diversion of the faeces. The study described here was designed to investigate the healing and long-term anastomotic strength after a standard left colon resection and anastomosis with concomitant proximal diverting colostomy.

Material and methods

Wistar male rats (135) with an initial weight of 230–270 g were used. Of these, 104 animals were randomly allocated to left colon resection with (colostomy group) or without (non-colostomy group) proximal diverting colostomy. Sixteen unoperated weight-matched animals were used for determination of the breaking strength of the intact left colon at the beginning or end of the study. Fifteen animals were used for studies of collagen synthesis.

The animals were kept in separate cages with four animals in each and with free access to water and a standard laboratory rat pellet diet.

In 119 animals laparotomy was performed under general anaesthesia (chloral hydrate, 25 mg/100 g body weight intraperitoneally (IP)) through a midline incision. A left colon resection 8–10 mm in length was performed 2·5–3·0 cm above the peritoneal reflection A standardized anastomosis was constructed with a single layer of eight interrupted inverting full-thickness 7-0 polypropylene (Prolene®, Ethicon Ltd., UK) sutures (*Figure 1*).

In the colostomy group the left colon resection was combined with a proximal diverting colostomy. The colon was transected at the major flexure with careful preservation of the marginal vessels and exteriorized in the upper part of the laparotomy incision. The colostomy was sutured in two layers with interrupted non-absorbable sutures to fascia and skin. Faecal content in the distal colon above the anastomosis was emptied in a retrograde direction and the distal colostomy end was closed with non-absorbable interrupted sutures and placed within the peritoneal cavity (*Figure 1*)

The postoperative weight development was recorded. Groups of animals were killed on postoperative days 2, 4, 7, 14, 28 and 56 by open chest cardiac puncture under general anaesthesia (chloral hydrate IP). Blood thus drawn was analysed for haemoglobin and albumin concentrations (g/l) according to hospital routine methods. After assessment of gross anastomotic complications the anastomosis was carefully dissected free from eventual adhesions and the anastomotic diameter *in situ* measured with the use of a caliper After removal, the colonic segment with the anastomosis in the middle was clamped in a specially constructed tensiometer. The anastomotic strength with sutures in place was determined The force at rupture was registered.

After the breaking strength test the sutures were removed and two segments 5 mm in length (colon segments 4 and 5) were cut on each side of the anastomosis. The segments were dried to constant weight in an oven at 100°C. The dry weight (mg) was measured and the specimens hydrolysed by 6 M HCl for 6 h. Hydroxyproline was determined by the method described by Stegemann and Stalder[9] The hydroxyproline content (μg/segment) and concentration (μg/mg tissue dry weight) could then be calculated.

As the results of tissue dry weight and collagen content were equal in the proximal and distal anastomotic segments the result is given as the sum of the two from each animal

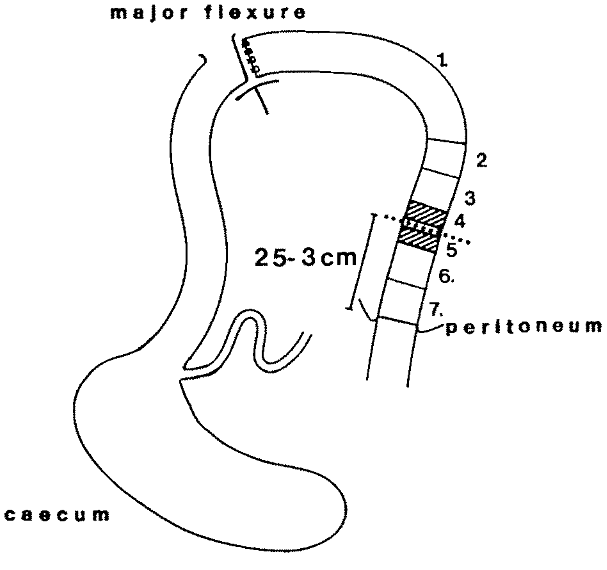

Figure 1 *Site of colostomy, anastomosis and studied colonic segments 1–7. Dotted line indicates site of anastomosis. Segment 1: Colon distal to site of colostomy and proximal to segment 2; Segments 2, 3 1 cm segments proximal to segment 4, Segment 4 0·5 cm segment proximal to anastomotic line, Segment 5. 0·5 cm segment distal to anastomotic line; Segments 6, 7· 1 cm segments distal to segment 5 down to peritoneal fold*

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Table 1 *Number of animals in anastomotic strength tests (those excluded are shown in parentheses)*

	Procedure	
Day	Resection	Resection and colostomy
0	8	–
2	8	8
4	7 (1)	8
7	7 (1)	8
14	7 (1)	8
28	7 (1)	7 (1)
56	7 (1)	8
Total	51 (5)	47 (1) Combined total 98 (6)

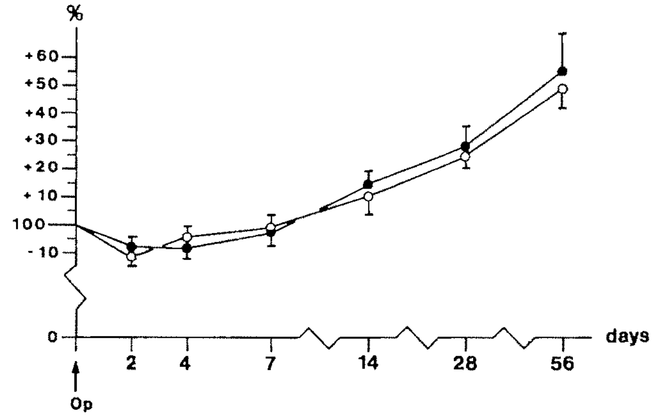

Figure 2 *Postoperative weight development as a percentage of initial body weight. ●, Animals with left colon resection; ○, animals with left colon resection and colostomy. The initial weight of operated animals was 253·0 ± 19·6 g (n = 104) Terminal weight in the non-colostomy group was 389·4 ± 27·1 g; +53·9 per cent (n = 7) and in the colostomy group 374·2 ± 25·6 g; +47·9 per cent (n = 8)*

The breaking strength of intact colonic wall in non-operated animals was measured in the colonic segment corresponding to the anastomotic site.

Collagen synthesis

In 15 animals (8 non-colostomy, 7 colostomy) the collagen synthesis on postoperative day 4 was studied in colonic segments 1–7 (*Figure 1*). Twenty-four hours before investigation the animals were given 200 μCi L-proline (2-3-4-5-^{3}H) (New England Nuclear, specific activity 100–120 Ci/mmol) intravenously in the tail. The incorporation of [^{3}H]proline into collagen was determined according to the method of Juva and Prockop[10] as applied in colonic healing by Jiborn *et al.*[11]. The specific activity of [^{3}H]hydroxyproline (d p.m. [^{3}H]hypro/μmol hypro) was taken as a measure of newly synthesized collagen..

Anastomotic complications

Anastomotic abscess and dehiscence as well as excessive dilatation (>10 mm) of proximal anastomotic segments were considered to be anastomotic complications and these animals were excluded from further study (*Table 1*)

Statistical methods

The mean and standard deviation were calculated. Comparisons of the means were carried out by Student's *t* test for unpaired observations. Comparison of complication rates was carried out by use of the χ^2 test with Yates' correction.

Results

Postoperative weight development (Figure 2)

The postoperative weight development was equal in both groups.

Nutritional assessment

There was no significant postoperative difference in either haemoglobin or albumin concentration between the groups.

Postoperative stools

In the non-colostomy group, stools were regularly noted on postoperative days 2–4. In the colostomy group, function of the colostomy was usually assumed after 1–3 days.

Anastomotic complications

In the non-colostomy group five animals had anastomotic complications. Three of these animals eventually died on postoperative days 8, 9 and 17. In the colostomy group one anastomotic complication occurred. The difference between the two groups is not statistically significant ($P > 0·05$).

Anastomotic diameter (Figure 3)

In the non-colostomy group, the anastomotic diameter increased significantly in the early postoperative period and remained wider throughout the study period.

In the colostomy group the anastomotic diameter stayed unchanged from the time of anastomotic construction.

Tissue dry weight

During the first 7 days the dry weight of the anastomotic segments was increased in both groups. In the non-colostomy group the dry weight remained elevated, whereas in the colostomy group it returned and stayed within the range of pre-operative values.

Hydroxyproline content (Figure 4)

The postoperative increase of hydroxyproline content in anastomotic segments was both earlier and considerably greater in the non-colostomy group.

In the non-colostomy group the hydroxyproline content was increased already on day 4 and a further marked increase occurred between days 4 and 7; from this day on, only a small increase was noted. In the colostomy group an increase of hydroxyproline content was not noted until day 7. From this day on, no further increase was observed.

In relation to the value at operation the hydroxyproline content on postoperative days 7 and 56 was approximately doubled and tripled respectively in the non-colostomy compared with the colostomy group.

Hydroxyproline concentration

In the non-colostomy group the hydroxyproline concentration was reduced on postoperative days 2 and 4, from where it returned and stayed within the limits of the initial value.

In the colostomy group no decrease of hydroxyproline concentration was seen in the early postoperative period.

Anastomotic strength (Figure 5)

The strength of the newly constructed left colon anastomosis was about one-third (1·93 ± 0·26 N) of the breaking strength of non-operated left colon (5·44 ± 0·67 N, $n = 8$).

In both groups the anastomotic strength decreased by about

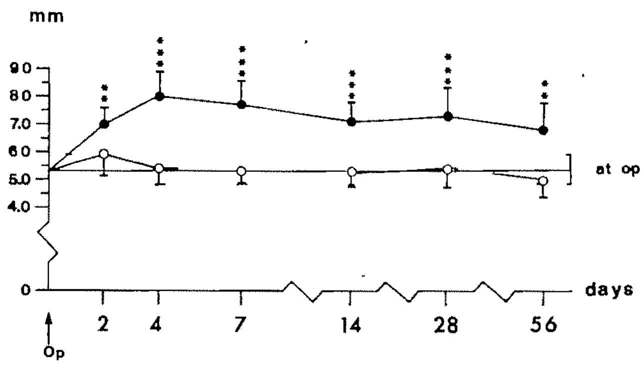

Figure 3 *Anastomotic diameter on postoperative days 2–56 in relation to value at operation. ●, Non-colostomy group, ○, colostomy group. **P<0·01, ***P<0·001*

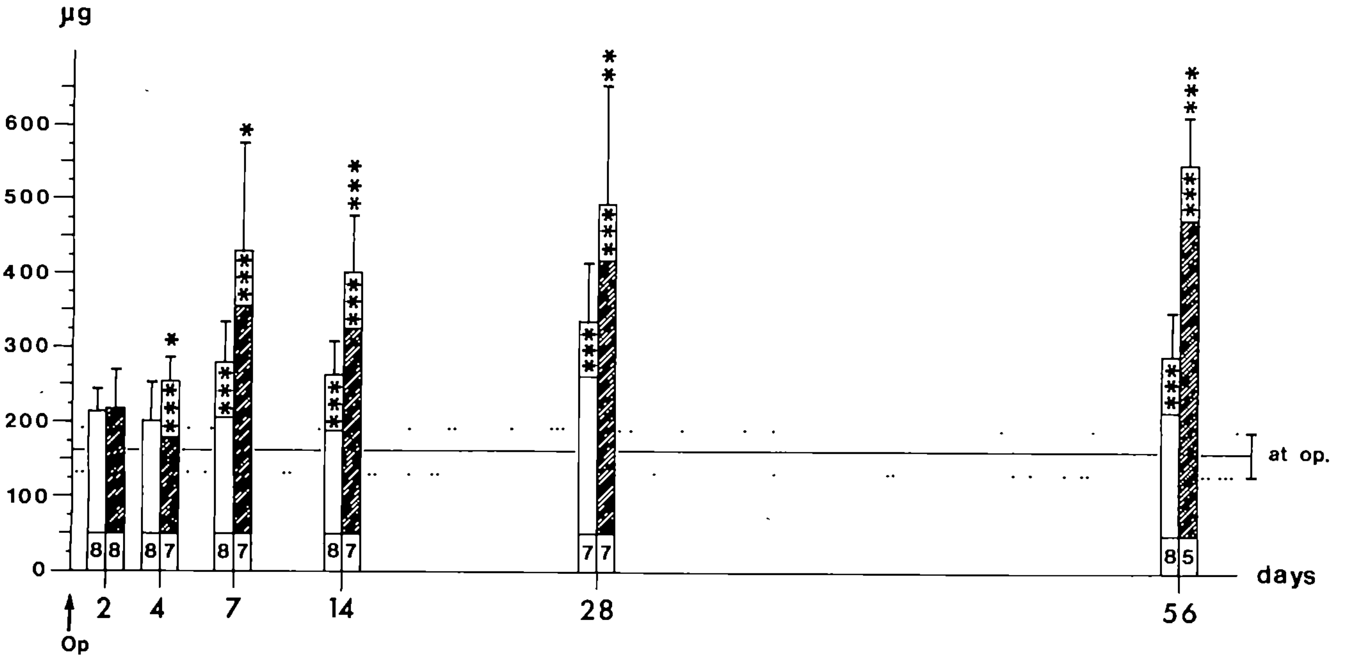

Figure 4 *Hydroxyproline content in anastomotic segments on postoperative days 2–56 in relation to value at operation.* ▨, *Non-colostomy group;* ☐, *colostomy group. Asterisks above bars denote statistical significance between groups, asterisks within bars denote statistical significance in relation to value at operation* (*$P<0{\cdot}05$; **$P<0{\cdot}01$; ***$P<0{\cdot}001$). *Numerals below bars show number of observations*

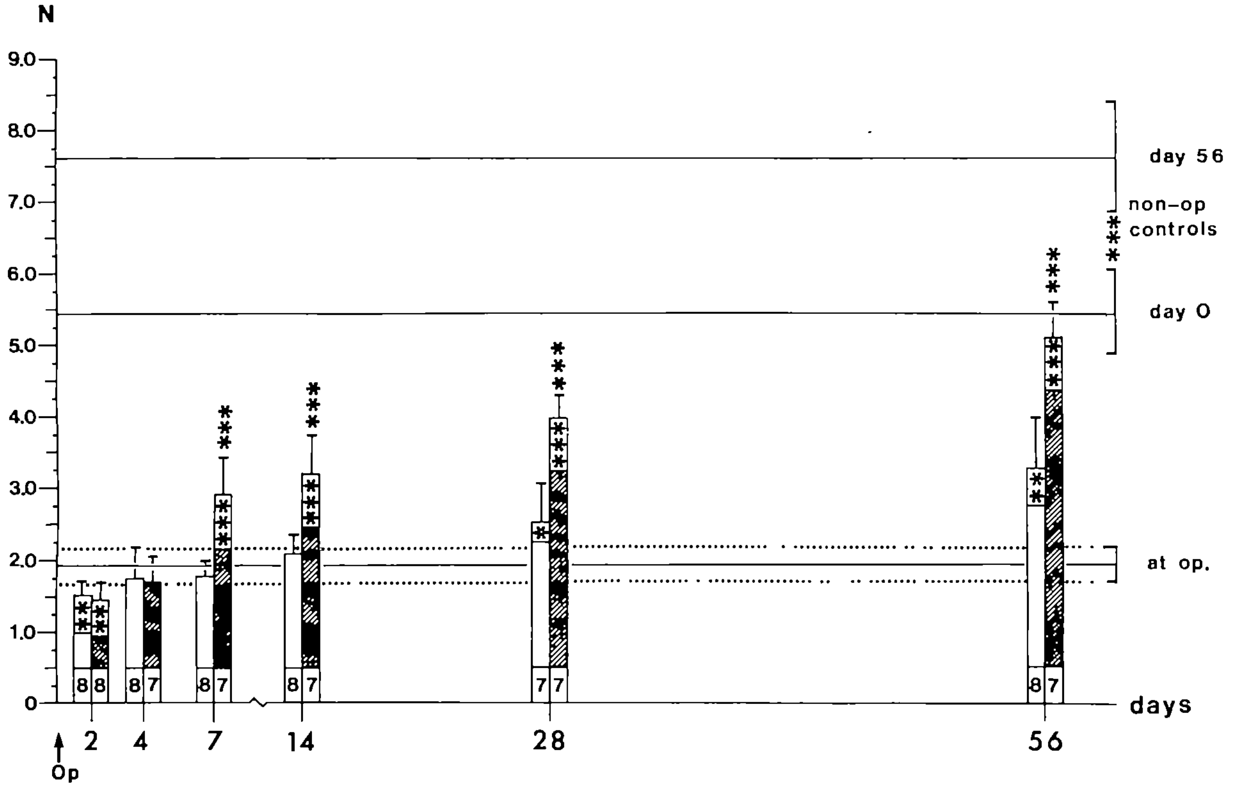

Figure 5 *Anastomotic strength development after left colon resection (non-colostomy group,* ▨*) and left colon resection with proximal diverting colostomy (colostomy group,* ☐*), in relation to value at operation. Asterisks above bars denote level of statistical significance between groups; asterisks within bars denote that in relation to initial (day 0) value* (*, **, *** *as in* Figure 4). *Numerals below bars show number of observations. Upper horizontal lines indicate breaking strength of left colon corresponding to the anastomotic site in weight-matched, non-operated controls*

25 per cent on postoperative day 2. At postoperative day 4 the anastomotic strength in both groups had returned to initial values.

In the *non-colostomy* group there was a rapid gain of anastomotic strength between days 4 and 7 (+67·6 per cent). A successive gain of anastomotic strength occurred during the remaining study period but at a slower rate.

In the colostomy group there was no increase in anastomotic strength from day 4 until day 28. A minor strength gain occurred in the late postoperative period.

In relation to the strength of the newly constructed left colon anastomosis, the anastomotic strength in the *non-colostomy* group had more than doubled after 56 days. In the *colostomy* group the corresponding increase was about 70 per cent.

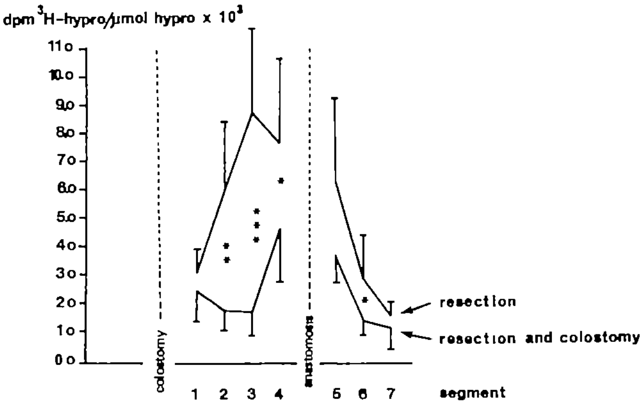

Figure 6 *Collagen synthesis in perianastomotic segments 1–7 of the left colon 4 days after left colon resection with or without concomitant proximal diverting colostomy. Asterisks denote level of statistical significance between groups* (*, **, ***, *as in* Figure 4)

After 56 days the anastomotic strength in the *non-colostomy* and *colostomy* groups respectively, had reached 68 and 43 per cent of the strength of intact left colon of weight-matched, non-operated controls.

Collagen synthesis (Figure 6)

In the *non-colostomy* group the collagen synthesis rate was markedly elevated both in the anastomotic region and proximal to it. The synthesis rate was elevated in the *colostomy* group but to a lower level and confined to the immediate vicinity of the anastomosis.

Discussion

Earlier investigations of colonic adaptation after defunctioning colostomy have disclosed hypoplastic mucosal changes[12] with massive reductions of crypt cell production rate[13] and mucosal RNA, DNA and protein content[14]. Blomquist[15] studied the effects of defunctioning colostomy upon the collagen metabolism of the left colon. After 11 days the collagen synthesis rate was found to be depressed by 57 per cent. An approximately 55 per cent reduction of the collagen content of the left colon was found after 28 days. In this study we have examined the long-term anastomotic collagen accumulation and its influence upon the anastomotic strength development after left colon resection with anastomosis and concomitant proximal diverting colostomy. We chose to measure the breaking strength of the anastomoses with the sutures in place in order not to damage the anastomosis by removal of sutures and because, in colonic healing in the rat, the anastomotic strength is not influenced by remaining sutures after 7 days[8].

After left colon resection and anastomosis there is usually a marked reduction of anastomotic strength to about 50 per cent of initial values during the early postoperative period[16]. The rather small decrease on day 2—about 25 per cent—of anastomotic suture holding capacity seen in the study described here may be explained by inclusion of more tissue in the sutures. Absence of decreased anastomotic suture holding capacity when sutures are placed at a distance of 3 mm or more from the anastomotic wound edge has previously been reported[17,18]. During the first 4 days there was no difference in the postoperative anastomotic strength between investigated groups. Marked differences in the anastomotic strength development were then noted. After 14 days a minor increase was found in the colostomy group, but a 60 per cent increase occurred in the non-colostomy group starting at 7 days. In the latter group this increase continued and the anastomotic strength at the end of the study was more than doubled. Nevertheless, the anastomotic strength was still only 68 per cent of the strength of unwounded colonic wall, an observation consistent with earlier findings[19]. In the colostomy group the increase of anastomotic strength was less pronounced but exceeded the initial value by 70 per cent after 56 days. The number of anastomotic complications was higher in the non-colostomy than in the colostomy group. Although not statistically significant, the difference might suggest protection of the anastomosis by proximal colostomy.

During the first week a rise of tissue dry weight was noted in both groups. It may be speculated that this rise depends on the inflammatory phase of healing with exudation of plasma proteins, deposition of fibrin and invasion of mesenchymal cells[20]. Continuous stimulation by faecal bulk sustained this rise whereas total bowel rest by proximal colostomy led to a return to initial values.

Anastomotic strength is mainly dependent upon collagen in the anastomotic line and bowel wall.[21–23]. The hydroxyproline content around the anastomosis in the non-colostomy group was increased by day 4 and doubled after 7 days. In the colostomy group the increase of hydroxyproline was delayed and smaller. At the end of the study, the accumulation of collagen was three times higher in the non-colostomy compared with the colostomy group. The increase in collagen around the anastomosis was earlier than the increase in anastomotic strength in both the non-colostomy and the colostomy group.

Even if different factors such as regulatory peptides (enteroglucagon)[24], epidermal growth factor[25] and the faecal bacterial flora[26] are all capable of influencing the maintenance of colonic epithelial cell mass, the most important factor seems to be the passage of intraluminal bulk[27,28]. The results of this study seem to bear out this statement, showing that total bowel rest by a proximal colostomy reduces the long-term accumulation of collagen in the anastomotic area with a reduced and delayed development of anastomotic strength.

In conclusion, this study showed that the accumulation of collagen around the anastomosis was slower to develop and less pronounced in those rats with a colostomy, while changes in anastomotic strength in the early postoperative period indicated that the collagen behaved in a different manner. Despite the delay in the development of anastomotic strength, the anastomotic healing was uncomplicated. Thus the findings in the study described here do not contra-indicate the use of a diverting colostomy.

Acknowledgements

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Multiple authorship

The Editors remain concerned about the number of papers submitted to the Journal which appear to carry an inappropriate number of authors. We whole-heartedly endorse the recent statement by the International Committee of Medical Journal Editors, namely that authorship 'should be based only on substantial contributions to (a) conception and design, or analysis and interpretation of data; (b) drafting the article or revising it critically for important intellectual content; and (c) final approval of the version to be published'. It must be stressed that these three criteria must *all* be fulfilled. Those submitting material to *The British Journal of Surgery* should be warned that the Editors intend to try to enforce these guidelines wherever possible.

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Role of collagenase in colonic anastomoses: a reappraisal

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Increased collagenolysis, with reduction in collagen concentration, has been incriminated in the breakdown of colonic anastomoses but previous studies have measured only collagen levels and non-specific collagenolytic activity. Collagenase, the initiating enzyme in collagen degradation, is synthesized on demand and controlled by tissue inhibitor of metalloproteinases (TIMP). Antibodies to collagenase and TIMP were applied to colonic anastomoses in rabbits to investigate the role of the enzyme during healing. Within 12 h of operation, secreting cells and extracellular collagenase were identified at the everted edges of the bowel wall. After 24 h, collagenase activity was accompanied by TIMP secretion in the same localized regions, and by the third postoperative day very few cells were still synthesizing enzyme in these areas, although extracellular activity remained visible. TIMP-secreting cells, however, were seen in a layer of connective tissue sealing the serosal surface of the anastomosis. At 7 days, both enzyme and inhibitor were found only in small aggregates of secreting cells in the deeper layers. The localization and extent of collagenase and TIMP activity accorded well with a normal healing response as, at all times, the enzyme was confined to the immediate vicinity of the suture line.

Keywords: Collagenase, tissue inhibitor of metalloproteinases, anastomosis, colon

Dehiscence of a large bowel anastomosis is a major complication of colonic surgery, prolonging hospital stay and increasing mortality from 7 per cent to 22 per cent[1]. Collagen is the major structural protein of the colon wall and excess collagenase activity was first implicated in the dehiscence of colonic anastomoses by indirect evidence from measurements of bursting pressure and of collagen. Collagen concentration in the colon wall decreases in the early postoperative period[2–4], reaching a trough after 48 h in rabbits. This corresponds to the time when the anastomosis is at its weakest. The assumption that the fall in collagen was due to an increase in collagenase was supported by Hawley[6], who showed that explants of normal colon produced greater lysis of collagen gels than did other parts of the gastrointestinal tract and confirmed a 145 per cent increase in collagenolytic activity 3 days after a colonic anastomosis.

Such lysis, however, may be due to a variety of proteolytic enzymes and is not specific to collagenase, the metalloproteinase which normally initiates extracellular collagen breakdown[7]. Increased understanding of collagenolysis has shown that mammalian collagenase has a very precise action, cleaving the triple helix at a single locus to produce three-quarter and one-quarter fragments which are then susceptible to degradation by other proteinases and cathepsins. Collagenase is secreted on demand, in a latent form, and must be activated extracellularly. Tissue inhibitor of metalloproteinases (TIMP), found in most tissues and cells in culture, forms a tight complex with the activated enzyme and regulates its activity by rapid inhibition[7].

This investigation has therefore employed immunolocalization techniques, using specific antibodies to collagenase and TIMP, to determine the precise *in vivo* distribution of this metalloproteinase and its inhibitor after colonic anastomosis in the rabbit.

Materials and methods

Preparation of tissue

Segments of colon 2 cm in length were resected from a standard site in the distal colon of 11 female New Zealand White rabbits (weight 1·5–2·5 kg), under pentobarbitone anaesthesia. Single-layer, everted anastomoses were then carried out with interrupted 6/0 silk sutures Getzen and Holloway[8] have demonstrated better healing with eversion than inversion in dog colon anastomoses and subsequent animal experiments have provided evidence in favour of both options, although clinical trials indicate that inversion produces less complications in man[9] However, inversion in our hands created a variable degree of obstruction in some rabbits; since obstruction considerably alters the collagen dynamics during colonic healing[3], a reproducible everted anastomosis was employed so that uncomplicated healing could be investigated.

Two animals were killed 12 h after operation and three each after 24 h, 3 days and 7 days. At the time of death a 2-cm segment containing the anastomosis at its centre, and 2-cm segments proximal and distal to this, were removed. Resected and postoperative segments were washed in five changes of Hank's balanced salts solution containing antibiotics and cut into 3-mm strips One strip of tissue from each segment of colon was fixed immediately in formalin for staining with haematoxylin and eosin The other strips from each segment were processed entirely for histochemistry as follows: alternate strips were orientated on Millipore filters, embedded in 7 per cent gelatin and snap-frozen for 90 s in liquid nitrogen; remaining strips were cultured for 3 h in Dulbecco's modification of Eagle's medium, containing 5 μM monensin and antibiotics, before embedding in gelatin and freezing as before. Monensin prevents the translocation of secretory proteins, including collagenase[10], and the consequent intracellular accumulation assists the identification of synthesizing cells. In this way the entire circumference of the bowel was examined for a distance of 3 cm from the suture line in each direction.

Immunolocalization

Frozen sections, 4–7 μm thick, were cut from each tissue block, fixed for 30 min in 4 per cent paraformaldehyde in phosphate buffered saline (PBS) and washed in three changes of PBS (5 min each wash). The tissue was made permeable with 0·1 per cent Triton X-100 for 5 min to allow the antibodies to penetrate into cells The tissue was then washed and treated for 10 min with 4-chloronaphthol (2·8 mM in methanol/PBS with 0·01 per cent H_2O_2), to prevent the non-specific binding of fluorescein by inflammatory cells[11]. After further washing, sections were incubated in a moist atmosphere for 30 min with 5 μg of anti-collagenase IgG[12], anti-TIMP IgG[13], or non-immune sheep serum IgG[14] to act as controls for non-specific staining. The anti-collagenase and anti-TIMP IgG were prepared by the immunization of sheep with purified preparations of either rabbit collagenase or rabbit TIMP. Specificity of these antisera and their use in other immunolocalization studies have

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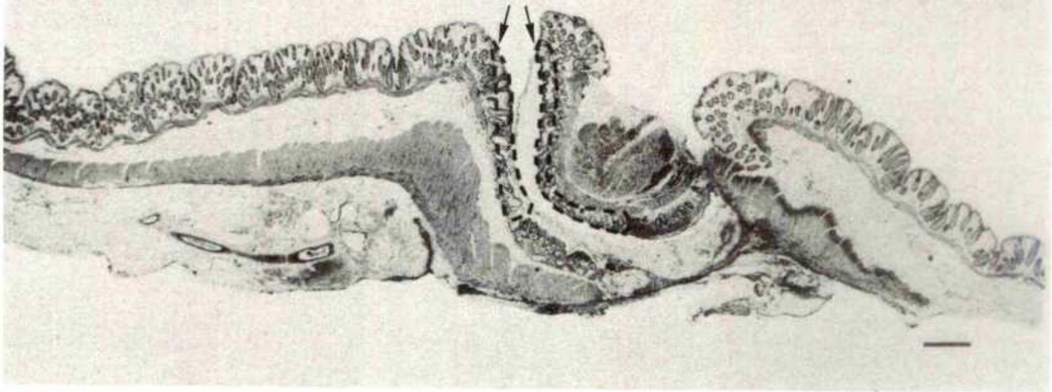

Figure 1 *Haematoxylin and eosin photomicrograph of colonic anastomosis 12 h after operation. Dotted outlines show extent of regions in which collagenase was localized. Bar = 500 μm*

been described previously[12,13]. Excess antibody was washed off and 2·75 μg of FITC-labelled pig anti-sheep antibody[14] applied for 30 min. Sections were treated with the nuclear counter-stain methyl green, 1 mg/ml for 2 min, and mounted in glycerol/PBS mounting fluid containing additives to reduce fading (Citifluor Ltd., London, UK). Slides were examined by epifluorescence with either a Leitz Dialux 20 photomicroscope or a Zeiss Photomicroscope III, using standard wide and narrow band filters. Fluorescent photomicrographs were taken on Kodak Ektachrome 400 film, uprated to 1600 ASA, and haematoxylin and eosin photomicrographs on Plus X Pan black and white film.

Results

All rabbits were healthy at the time of death and no anastomotic dehiscence was seen. The histochemical findings were consistent around the circumference of each anastomosis and were reproducible in different animals investigated at the same time after operation. The staining patterns proximal and distal to the suture line were similar at all postoperative stages.

Resected colon

No green immunofluorescence localizing collagenase or TIMP was seen in any of the segments of normal colon resected at operation and culture with monensin did not show any secreting cells. Inflammatory cells were seen to have yellow granules after treatment with 4-chloronaphthol.

Twelve hours after operation

Twelve hours after operation the gap between the two ends of bowel was filled with clot and fibrin and early inflammatory cell infiltration was seen. The region of the anastomosis showed positive immunofluorescence for collagenase which was exclusively localized in the everted portions of bowel wall (*Figure 1*). The entire length of the everted parts contained extracellular enzyme on the interstitial matrix between the superficial mucosal crypts (*Figure 2a*). Many actively secreting cells, with fine speckles of fluorescence in the perinuclear region, could be identified without the need for short-term culture with monensin (*Figure 2b*). Some extracellular enzyme was also present in the vicinity of suture material.

Very little TIMP was visible 12 h after anastomosis, in any area of colon. No staining was seen with either antibody outside the everted regions or in the immediate vicinity of the suture line.

Twenty-four hours after operation

Twenty-four hours after operation the gap between the bowel ends was still plugged with fibrin and a greater inflammatory infiltrate was present. Extracellular collagenase was seen in the everted regions but was more discretely localized than at 12 h since it was confined more closely to the cut ends. At these sites the enzyme spread more deeply through the tissue layers into the submucosa and into the fibrin plug (*Figure 3*). Cells secreting collagenase were fewer and could only be identified after culture with monensin.

However, TIMP staining was seen at 24 h and was found in the same regions as collagenase. The distribution of TIMP closely paralleled that of collagenase, and TIMP-secreting cells (*Figure 2c*) were similarly visible after monensin treatment.

Three days after operation

By the third postoperative day the fibrin plug filling the space between the two ends of bowel was larger and inflammatory cells were concentrated around the tips of the everted bowel ends. The serosal surface was completely sealed across the gap by a distinct layer of connective tissue over the plug (*Figure 4*). Extracellular collagenase was once more found in the everted regions of the wall, adjacent to the inflammatory infiltrate, and very few collagenase-secreting cells could be found, even after monensin treatment. Extracellular enzyme was still present around suture material.

TIMP distribution paralleled that of collagenase but, in addition, cells secreting TIMP were found within the layer of connective tissue which sealed the serosal surface of the anastomosis (*Figure 2d*). A chain of secreting cells stretched within this thickened protective layer to the point where it narrowed into the normal serosal coat of the bowel wall. No extracellular TIMP or intra- or extracellular collagenase was seen in this layer.

Seven days after operation

One week after anastomosis the healing process had advanced sufficiently in some areas to restore mucosal continuity. In the deeper layers, the plug was organized into maturing fibrous tissue but occasional buried mucosal crypts and suture remnants could still be identified (*Figure 5*). Around these scattered remnants, and in small areas within the fibrous tissue, were aggregates of cells containing collagenase (*Figure 2e*) and cells containing TIMP (*Figure 2f*) which were visible in both monensin-treated and uncultured tissue. Little extracellular enzyme or inhibitor was seen in any area.

Discussion

This histochemical study used specific antibodies to collagenase and TIMP to investigate their distribution in colon during the first week after anastomosis. As with previous studies[12], neither collagenase nor TIMP could be localized in normal colon which had been resected at operation but within 12 h of anastomosis collagenase was visible both in secreting cells and extracellularly. Synthesis occurred in those areas closest to the sites of damage, the cut edges and the regions penetrated by the

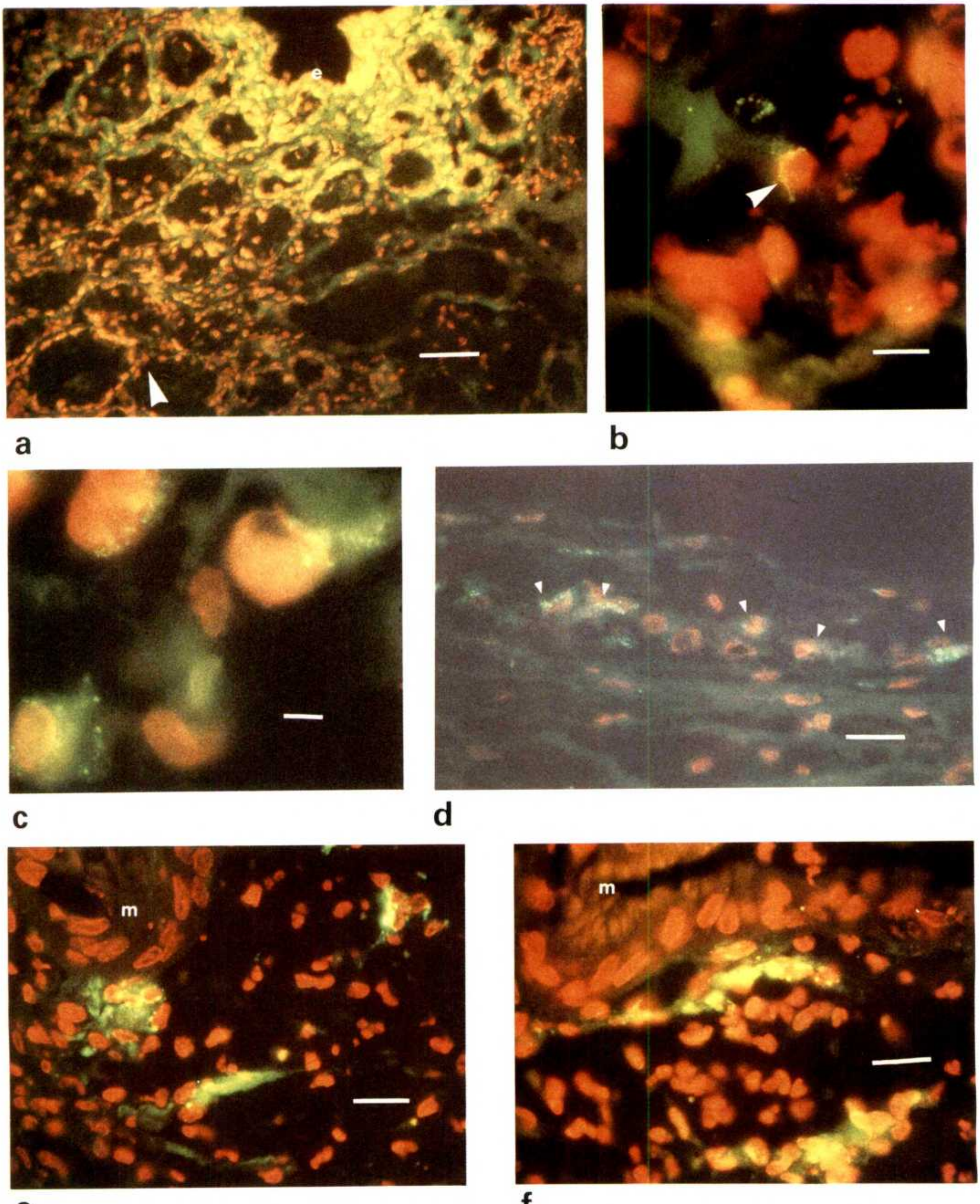

Figure 2 *Immunofluorescence of collagenase and TIMP in rabbit colon anastomoses.* **a** *Mucosa from everted region of anastomosis 12 h after operation; treated with anti-collagenase. Red nuclei outline the mucosal crypts. In the upper part of the picture green fluorescence shows collagenase on the interstitial matrix, extending only 350 μm from the epithelial surface (e). Arrow indicates interstitial matrix not staining for collagenase, confirming very localized distribution of this enzyme. Bar = 50 μm.* **b** *Everted region of anastomosis 12 h after operation; incubated with monensin and treated with anti-collagenase. Green fluorescence identifies intracellular collagenase granules around the red nucleus of a secreting cell (arrow) and in the adjacent extracellular space. Bar = 10 μm.* **c** *Everted region of anastomosis 1 day after operation; incubated with monensin and treated with anti-TIMP. Green fluorescence shows TIMP granules in the perinuclear regions of three secreting cells. Bar = 5 μm.* **d** *Connective tissue layer sealing serosal surface of anastomosis 3 days after operation; incubated with monensin and treated with anti-TIMP. Many red nuclei are surrounded by bright green granules (arrows) forming a chain of TIMP-secreting cells within this serosal layer. Bar = 20 μm.* **e** *Anastomotic region 7 days after operation with buried mucosal remnant (m); treated with anti-collagenase. Collagenase-secreting cells cluster around the outside of the mucosal remnant. Bar = 20 μm.* **f** *Anastomotic region 7 days after operation, with same mucosal remnant as* **e** *a few sections further into block of tissue; treated with anti-TIMP. Groups of TIMP-secreting cells are also seen around the buried mucosa (m). Pale red nuclear ghosts indicate cell death within the remnant. Bar = 20 μm*

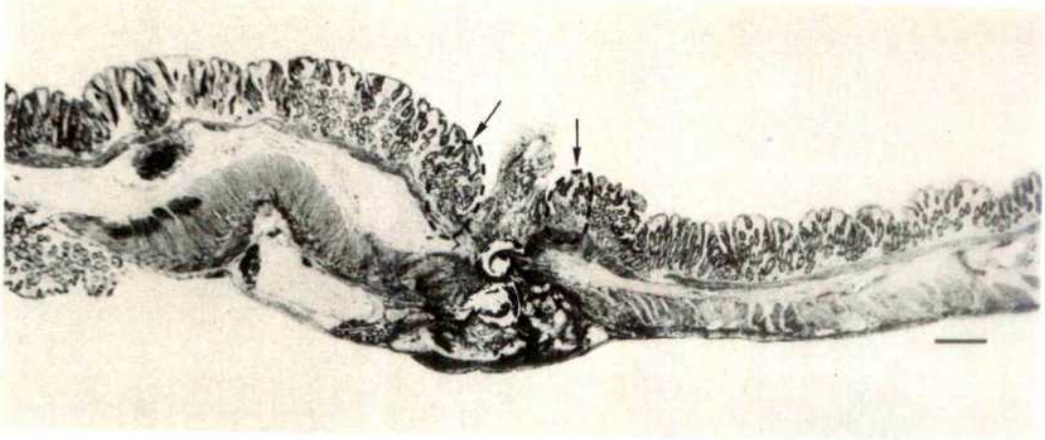

Figure 3 *Haematoxylin and eosin photomicrograph of colonic anastomosis 24 h after operation. Dotted outlines show extent of regions in which collagenase and TIMP were localized. Bar = 500 µm*

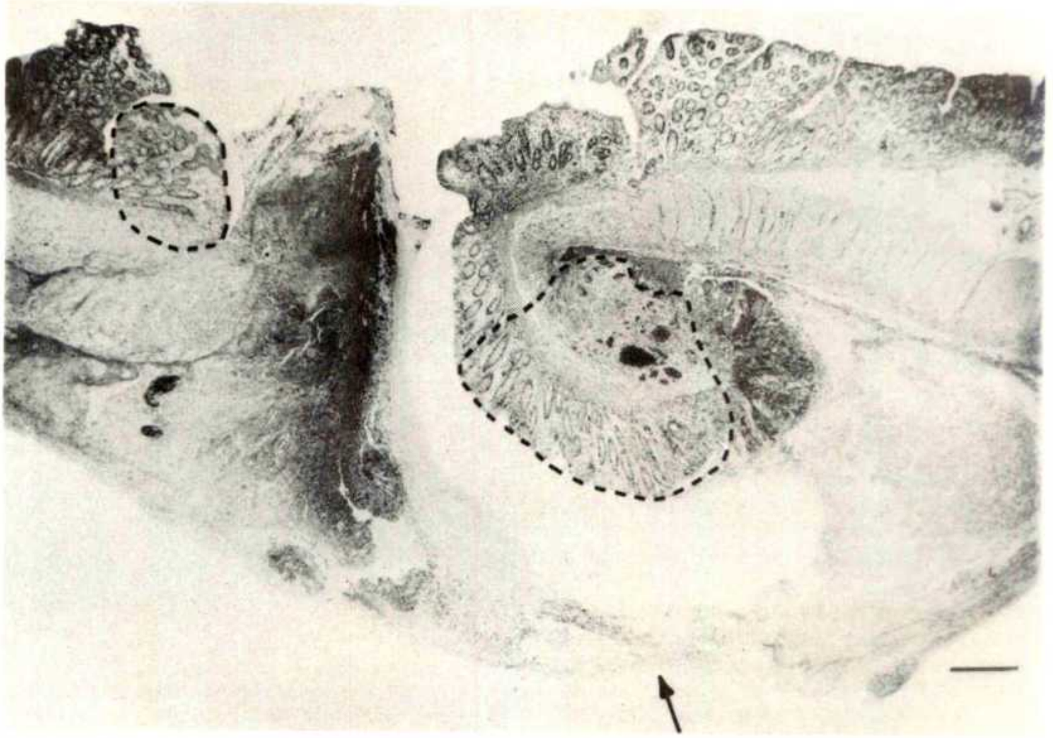

Figure 4 *Haematoxylin and eosin photomicrograph of colonic anastomosis 3 days after operation. Dotted outlines show extent of regions in which collagenase and TIMP were localized. TIMP cells were also found in connective tissue layer on serosal surface (arrow). Bar = 500 µm*

sutures. Collagenase synthesis and secretion appeared first in the mucosal layers of the everted bowel wall. During the course of healing and remodelling, these everted parts will be removed to restore the alignment of the tissue layers and collagen breakdown is an essential part of this process.

By 24 h the collagenase distribution was less extensive and was accompanied by TIMP. The degradative process now appeared to be under tight control since the inhibitor rapidly inactivates the enzyme and is thought to be produced by cells to regulate the extracellular activity of collagenase and other metalloproteinases[7]. This parallel localization of TIMP and collagenase was seen at all subsequent times. The process of removing the everted regions continued through the third postoperative day, with collagenase and TIMP appearing to precede the inflammatory cells as they progressed deeper into the tissue. Connective tissue formation was seen in a thickened layer on the serosal surface, sealing the peritoneal cavity from the lumen of the bowel until the underlying fibrin had been replaced by more substantial scar tissue. TIMP secretion, without any evidence of collagenase, was found within this layer, and probably contributes to the maintenance of anastomotic integrity by preventing premature degradation of this protective coat.

At 7 days after operation the fibrin plug had been replaced by a collagenous scar which had still to mature and contract. Remnants of undegraded mucosa and other tissues were seen adjacent to small groups of cells secreting collagenase and TIMP. This is similar to the findings in hypertrophic skin scars[15], where regions of active remodelling contained collagenase and TIMP in close proximity to negative, inactive regions. A similar sequence of changes was seen, on a smaller scale, around the sites of damage created by suture material. This very localized remodelling is likely to continue for some time, until normal tissue organization has been fully restored.

Although granulocytes have been proposed as the source of collagenase responsible for the loss of collagen from colonic anastomoses[16], there is no definitive evidence in the literature for a specific collagenase in rabbit polymorphonuclear leucocytes and neither a specific collagenase nor a TIMP-like collagenase inhibitor was detectable in rabbit polymorphonuclear leucocytes in this laboratory (U. Bretz and G. Murphy, unpublished observations). The secreting cells in this study had

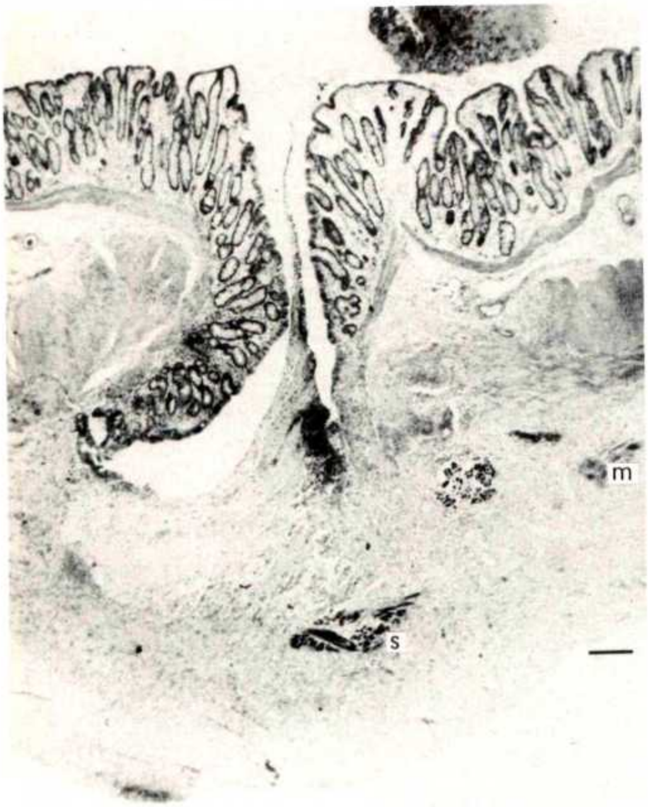

Figure 5 *Haematoxylin and eosin photomicrograph of colonic anastomosis 7 days after operation. Cells secreting collagenase and TIMP were found alongside buried mucosal remnants* (m) *and residual suture material* (s). *Bar = 200 μm*

the appearance of fibroblasts and enzyme was localized in areas which were only later infiltrated by inflammatory cells. The stimulus for synthesis may come from the secretion of cytokines, such as interleukin 1, by inflammatory or connective tissue cells[7], while the damaged tissue itself releases plasmin, a collagenase activator.

The sequence of events which has been outlined is that of an uncomplicated healing reaction and the locations and extent of collagenase production are those that might be predicted in a normal healing response. Hendricks and colleagues[5] measured the collagenase concentration of the colon wall following uncomplicated anastomosis in the rabbit and found a 38 per cent decrease by 48 h; this significant fall extended for several centimetres along the colon in a proximal direction[2,3]. However, in this study we found no collagenase localized in the bowel wall more than a few millimetres from the cut edge, either proximally or distally: both collagenase and TIMP were confined to the immediate vicinity of the suture line at all times. These findings suggest that the apparent decrease in collagen concentration is not due to extensive collagenase activity.

The role of collagenase appears to be to initiate the breakdown of tissue which is now redundant and would interfere with the restoration of continuity. This tissue can then be further degraded and removed by inflammatory cells. This investigation, however, has been confined to uncomplicated anastomoses and the enzyme distribution in circumstances of dehiscence has yet to be determined. These methods can now be applied to situations in which anastomotic breakdown is more likely, such as ischaemia or peritonitis, to show whether the production of collagenase is then more extensive or the balance between enzyme and inhibitor is lost. Although the administration of proteinase inhibitors appeared to improve anastomotic healing in animals[17–19], the results of a clinical trial were less convincing[20]. This study indicates that little benefit is to be expected from a specific inhibition of collagenase in uncomplicated anastomoses, since the enzyme is already closely controlled by TIMP. However, if in further studies the balance between collagenase and TIMP is shown to be disturbed during anastomotic dehiscence, then the administration of synthetic TIMP-like inhibitors might be a valuable therapeutic measure.

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Resectability rate of hepatocellular carcinoma in rural southern Africans

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The purpose of this analysis was to ascertain the resectability rate of symptomatic hepatocellular carcinoma in rural southern African black males. All 224 such patients proven to have hepatocellular carcinoma in a single hospital were included in the study. Of 205 patients undergoing a complete diagnostic work-up, 134 ((65·3 per cent) were judged on clinical criteria to be inoperable, 23 (11·2 per cent) had pulmonary or osseous metastases, and 38 (18·5 per cent) proved on hepatic imaging and 5 (2·4 per cent) on hepatic arteriography to have an irresectable tumour. Thus, only five (2·4 per cent) of these patients proceeded to laparotomy. Another 7 patients who did not have an arteriogram, 9 with surgical emergencies, and 2 mistakenly believed to have an amoebic hepatic abscess also underwent laparotomy. Only 2 patients (0·9 per cent of 223) proved to have a resectable tumour. The extremely low resectability rate reinforces the urgent need for a surveillance programme to detect early tumours in high-risk members of this population.

Keywords: Hepatocellular carcinoma, resectability rate, hemihepatectomy

Surgical resection is the only curative treatment currently available for hepatocellular carcinoma (HCC). The frequency with which HCC can be resected depends upon the circumstances in which the tumour is diagnosed. If asymptomatic HCCs are detected in surveillance programmes designed to recognize small tumours in high-risk individuals, the majority of the tumours are operable, and a 60 per cent 5-year survival rate has been reported in one study[1]. However, when patients present, as the vast majority do, with symptoms attributable to HCC, far fewer resectable tumours are found. The operability rate then differs between populations, and depends upon such factors as the extent of the tumour burden, the biological characteristics of the tumour, including the frequency with which it is encapsulated and with which the fibrolamellar variant occurs, and its propensity for vascular invasion, as well as the prevalence of coexisting cirrhosis. 'Western' patients, with generally smaller and slower-growing tumours, have resectability rates which may be as high as 37 per cent[2], and Japanese patients, who often have a well-encapsulated tumour but in whom advanced cirrhosis is common, have rates of up to 20 per cent[3]. By contrast, only 8 per cent of Ugandan patients have resectable tumours[4]. Operability rates are also influenced by the source of the clinical material, patient selection resulting in surgical units generally reporting higher rates than physicians.

Our experience with southern African black people suggested that resectable HCCs were even rarer than in Uganda. A formal analysis of the operability rate in all black patients with HCC admitted to a single hospital was undertaken.

Patients and methods

A total of 224 patients proven to have HCC were admitted to a medium-sized hospital in Johannesburg over a 7-year period. The hospital is a tertiary care referral centre serving the gold-mining industry. Each of the regional hospitals in the industry was requested to transfer all patients with proved or even suspected HCC to the Rand Mutual Hospital. All of the patients studied were hospitalized with symptoms attributable to HCC, i.e. in none of the patients was an asymptomatic tumour detected in a surveillance programme of individuals at high-risk of developing HCC. A uniform approach to the diagnosis and management of the patients was possible because the medical and surgical staff of the hospital remained remarkably constant and M.C.K. was the consultant hepatologist to both services throughout the study. The patients were rural southern African black males originating from Mozambique, Transkei, Ciskei, Lesotho, Zululand, Malawi, Zimbabwe, and South Africa. The sex ratio of HCC in this population is 5–6 males to 1 female. The patients' ages ranged from 19 to 65 years with a mean of 39·2 years. In spite of the fact that the patients were all mine labourers, the age structure of the group is not dissimilar to that of all rural southern African black patients with HCC.

The patients were evaluated clinically at the time of admission to the Rand Mutual Hospital and the relevant blood samples were taken. All patients then had postero-anterior and lateral plain chest radiographs performed. When indicated, X-rays (and radionuclide scans) were also taken of relevant bones. No attempt was made to detect asymptomatic osseous metastases by radionuclide screening. Almost all of the patients were then submitted to one or more modalities of hepatic imaging. If indicated, a hepatic arteriogram was then performed. The diagnosis of HCC was confirmed histologically in all patients either on a percutaneous biopsy or at laparotomy or necropsy. As long as the patients were thought to have a resectable tumour, percutaneous biopsy of the liver was not performed.

A protocol was formulated using the following criteria of irresectability of the tumour.

Clinical criteria. There were two absolute clinical criteria of irresectability: clear evidence on palpation of involvement of both lobes of the liver by tumour, and very advanced disease (including hepatic failure, malignant cachexia, disseminated malignancy, a preterminal state, uncontrollable variceal haemorrhage, and irreversible hypoglycaemic coma). The presence of either was regarded as being indicative of inoperability. Relative clinical criteria of irresectability were deep or moderate jaundice, severe ascites, marked muscle wasting, and severe pedal oedema. The presence of two or more of these criteria was regarded as evidence of inoperability.

Metastatic spread. The presence of pulmonary or osseous metastases denoted spread of the tumour beyond the liver and hence inoperability.

Imaging of the liver. The liver was 'imaged' in almost every patient, using at least one and usually two or more modalities. The imaging modalities available at the Rand Mutual Hospital were ultrasonography, radionuclide scanning, and computed tomography. Evidence of tumour deposits in both lobes of the liver, the presence of tumour in such a position in relation to the hepatic vasculature as to indicate that resection would be imposssible, or the presence of tumour

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in portal or hepatic veins or the inferior vena cava denoted irresectability.

Hepatic arteriography. Those patients in whom the clinical features, radiological investigations, and hepatic imaging suggested that the tumour might be resectable usually underwent selective hepatic arteriography. The purpose of this investigation was threefold: to detect tumour deposits that were too small to be seen on hepatic imaging, to visualize the portal vein on delayed pictures, and to provide the surgeon with information about the hepatic vascular anatomy in the event that surgery was to be undertaken. In addition, information about the presence or absence of coexisting cirrhosis was obtained in some patients. Radionuclide and contrast venography were used to detect the presence of tumour in the inferior vena cava.

If the patient showed no clinical, radiological, imaging, or angiographic evidence of irresectability, and hepatic function was satisfactory (as judged by serum albumin, bilirubin and prothrombin concentrations), an exploratory laparotomy was performed in order to decide finally on the resectability of the tumour.

Eleven patients did not undergo the full diagnostic work-up for one of two reasons. In nine patients a surgical emergency was present at the time of admission or developed subsequently, and necessitated urgent intervention. In the other two patients laparotomy was performed in pursuit of the wrong diagnosis and HCC was only discovered at that time.

Serum α-fetoprotein (AFP) concentrations were measured by radioimmunoassay (Amersham Corp., UK), and hepatitis B virus surface antigen (HBsAg) and antibody (anti-HBs) and core antibody (anti-HBc) by radioimmunoassay (Ausria II, Ausab, Corab; Abbot Laboratories, North Chicago, Illinois, USA).

Results

Inoperable on clinical criteria. Of the 205 patients having a complete diagnostic work-up, 134 (65·3 per cent) were judged on clinical criteria to have an irresectable tumour. One hundred and six of these patients had clear evidence on palpation of involvement of both lobes of the liver (in 41 patients this was the only criterion of inoperability, and in 22 it occurred in association with advanced disease, in 26 with advanced disease and one or more relative criteria of irresectability, and in 17 with one or more relative criteria of irresectability). In order to validate our clinical assessment of involvement of both hepatic lobes by tumour, we correlated this finding with the extent of tumour on imaging and, where applicable, laparotomy. Of the 106 patients, 101 were submitted to hepatic imaging (4 of these also underwent laparotomy) and 2 were assessed only at laparotomy. In two patients imaging did not agree with the clinical assessment. At laparotomy in one of these, the clinical extent of the tumour was confirmed. In another five patients, it was not certain on imaging whether or not the tumour was resectable, and at laparotomy in one (done because of a subsequent severe haematemesis) the clinical assessment of involvement of both lobes was confirmed. In two patients in whom hepatic imaging confirmed the clinical impression of involvement of both hepatic lobes, this was confirmed at laparotomy performed in order to obtain tissue for diagnosis. In two patients having a laparotomy without undergoing imaging, the clinical assessment of tumour extent was confirmed. Thus, in only 1 of 103 patients may the clinical assessment of hepatic involvement have been incorrect (in a further four patients it was uncertain on imaging if the tumour was resectable or not).

Twelve patients had evidence of advanced disease, three with advanced disease alone (including one with irreversible coma resulting from hypoglycaemia) and nine with one or more relative criteria of inoperability in addition. The final 16 patients in the clinically inoperable category had two or more relative criteria of irresectability (deep or moderate jaundice and/or severe ascites and/or severe muscle wasting). Twenty-six of these twenty-eight patients underwent hepatic imaging. In 21 the tumour involved both hepatic lobes, and in the remaining 5 it was not certain whether or not both lobes contained tumour. None of these 28 patients proceeded to laparotomy.

Metastatic spread. Twenty-three of the patients who did not have clinical criteria of irresectability (11·2 per cent of the 205 patients) had either pulmonary (nineteen patients) or osseous metastases (four patients). An additional 28 patients who had already been judged on clinical grounds to be inoperable also had metastases (24 pulmonary alone, 2 osseous alone, and 2 both). One further patient presented with an isolated metastasis in the neck of the femur. This was thought by the orthopaedic surgeons to be a primary bone tumour and the upper end of the femur was resected and replaced by a prosthesis. When it was realized that the primary tumour was HCC, there were no clinical or imaging contra-indications to resection of the primary tumour, and the patient was therefore submitted to laparotomy. Unfortunately, the tumour proved at operation to be irresectable because, although the left hepatic lobe was uninvolved by tumour, there was extensive malignant infiltration of the diaphragm, and the liver was severely cirrhotic.

Inoperable on imaging. In 38 patients (18·5 per cent of the 205 patients) who were thought on clinical grounds to have an operable tumour and had no pulmonary or osseous metastases, both lobes of the liver were clearly shown to be involved by tumour or there was other evidence of irresectability on hepatic imaging. This was established using three imaging modalities in 7 patients, two in 26 patients, and one in 5 patients.

In 127 patients who were believed on clinical criteria to have inoperable tumours hepatic imaging was performed. Involvement of both hepatic lobes or other evidence of irresectability was shown in 113 of these patients. Three patients were thought to have resectable tumours on imaging criteria alone, and in the remaining eleven operability was uncertain. Nineteen patients rejected for surgery because of pulmonary or osseous metastases underwent imaging: fifteen had involvement of both hepatic lobes, and in the remaining four the extent of the tumour was uncertain.

A total of 202 patients underwent imaging of the liver. In 116 patients (57·4 per cent) a single mass-lesion was seen in the liver, and in 86 patients (42·6 per cent) two or more mass-lesions were present. The latter involved both hepatic lobes. Of the single lesions, 98 (48·5 per cent) appeared to be present predominantly, or much less often entirely, in the right lobe of the liver, and 18 (8·9 per cent) predominantly, or occasionally entirely, in the left lobe.

Inoperable on arteriography. Ten patients who were deemed operable on clinical criteria, did not have metastases, and who seemed to have a resectable tumour on imaging, underwent selective hepatic arteriography. Five of these (2·4 per cent of the 205 patients) were shown to have satellite nodules in the apparently uninvolved lobe of the liver which had not been detected on imaging. Of the remaining five, the tumour appeared to be resectable in four and in one it was not certain whether or not the tumour would be operable. Three additional patients underwent arteriography: in two this confirmed the impression on imaging of an inoperable tumour, and in one the tumour appeared clinically to be resectable and the imaging was doubtful, but on arteriography it proved to be irresectable.

Thus, of the 205 patients who underwent a complete diagnostic work-up, 134 (65·3 per cent) were rejected for surgery at a clinical level, 23 (11·2 per cent) had obvious metastases, 38 (18·5 per cent) were clearly shown on hepatic imaging to have tumour in both hepatic lobes or other reasons why they were ineligible for curative surgery, and five (2·4 per cent) were shown on hepatic arteriography to be irresectable. The remaining five patients (2·4 per cent)), together with eight additional patients who were operable on all criteria but did not have an arteriogram (a total of 6·1 per cent of 213 patients), were considered to be potentially operable. Hepatic function was good in these patients, and the presence of tumour in the inferior vena cava was excluded by radionuclide and contrast venography. Exploratory laparotomy was advised. One patient

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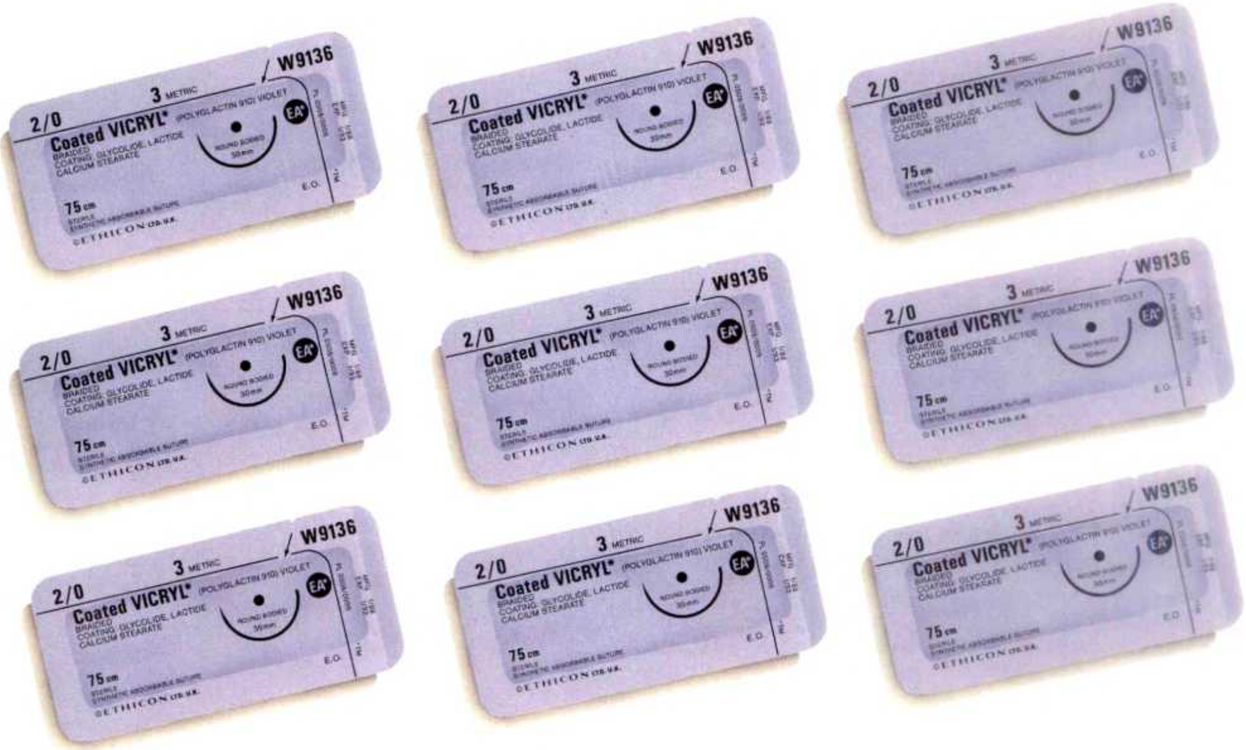
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Announcement

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Surgical Endoscopy, Ultrasound, and Interventional Techniques

Berlin, West Germany, June 29 – July 2, 1988

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The meeting will take place at the ICC in Berlin.

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For further information please send in the attached preliminary registration form to the Congress secretariat.

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Management of the Surgical Patient:
The Impact of Endoscopy, Ultrasound, and Interventional Techniques

Preliminary Program
The program will consist of morning plenary lectures and morning and afternoon sessions of free presentations. One afternoon is reserved for poster and video sessions.

Topics to be covered during the conference are:

- Endoscopy and Ultrasound in
  - gastrointestinal surgery
  - pancreatic, liver, biliary surgery
  - chest surgery
  - orthopedic surgery
- New Instruments and Techniques
  - angioscopy
  - laser
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International Congress on Surgical Endoscopy, Ultrasound, and Interventional Techniques held together with the **15. Symposium der Chirurgischen Arbeitsgemeinschaft für Endoskopie und Sonographie (CAES) der Deutschen Gesellschaft für Chirurgie.** **Berlin, June 29 – July 2, 1988**

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Other people interested (indicate address please):

refused surgery. The remaining 12 patients (5·7 per cent of 212 patients) were submitted to laparotomy.

Inoperable at laparotomy. Of the 12 patients undergoing laparotomy, the tumour proved to be irresectable in 11. The reasons for this were as follows. In six patients the tumour involved both hepatic lobes (in two of these the liver was also severely cirrhotic); in one it involved both lobes and there were in addition malignant glands in the porta hepatis; in two patients tumour was evident in both lobes, the liver was severely cirrhotic, and peritoneal metastases were present; in one patient the tumour affected only the right lobe of the liver, but there was extensive infiltration of the right hemidiaphragm, and the liver was severely cirrhotic; and in one patient advanced cirrhosis was present and the exact extent of the tumour could not be assessed. In one of the patients in whom tumour involved both lobes of a non-cirrhotic liver, it was initially thought at laparotomy that the tumour, although large, was confined to the right lobe. However, it proved impossible to remove the tumour completely and residual HCC remained in the left lobe.

Successful resection. One patient (0·5 per cent) underwent a successful left hemihepatectomy for a tumour confined to the left lobe of the liver. The non-tumorous liver was not cirrhotic and there was no discernible distant spread of the tumour. The patient was given epiadriamycin postoperatively. Ten months have elapsed since the operation and the patient remains well with no evidence of tumour recurrence.

Laparotomy without a full diagnostic work-up. In nine patients an emergency laparotomy was performed either because of an acute haemoperitoneum resulting from tumour rupture (six patients) or because of uncontrollable haematemesis (three patients). In two of the former patients the tumour appeared to be localized to one hepatic lobe: in one the non-tumorous hepatic tissue was not cirrhotic and in the other mild cirrhosis was present. The tumour was therefore resected in both patients. Thus, in the whole series of 223 patients with HCC, 3 (1·3 per cent) underwent tumour resection. In one of the two patients undergoing resection of a ruptured tumour, the serum α-fetoprotein level 7 days after the operation was 433 ng/ml and 1 month later it was 602 ng/ml. After another month the level had reached 16 713 ng/ml and hepatic imaging showed unequivocal tumour deposits. Clearly, resection had been incomplete (in effect, therefore, 2 of 223 patients (0·9 per cent) had a resectable tumour). The other patient remained completely well for 34 months. At this point he was readmitted with a recurrence of HCC, which proved to be extensive within the liver and which failed to respond to chemotherapy.

The other seven patients undergoing laparotomy for surgical emergencies proved to have irresectable tumours. In five, HCC was present in both lobes and the liver was severely cirrhotic; one had HCC in both lobes but no cirrhosis; and one had severe cirrhosis and it was difficult to assess the full extent of the tumour.

Laparotomy in pursuit of the wrong diagnosis. The remaining two patients underwent laparotomy with the intention of draining a suspected amoebic hepatic abscess. In each, HCC was found to be present and to occupy both hepatic lobes (the livers were not cirrhotic).

Laparotomy for other reasons. Twelve of the patients who had been judged on clinical grounds or on imaging to have an irresectable tumour nevertheless underwent laparotomy. One patient developed uncontrollable haematemesis, in one the tumour ruptured, and in ten laparotomy was performed to obtain tissue for definitive diagnosis. Inoperability was confirmed in each patient: eight had tumour deposits in both hepatic lobes and the liver was severely cirrhotic (one patient had peritoneal metastases in addition), and four had tumour deposits in both lobes but no cirrhosis.

α-fetoprotein

Of the 224 patients 21 (9·4 per cent) had a normal serum AFP concentration (< 20 ng/ml) and 35 (15·6 per cent) had a raised but non-diagnostic value (21–500 ng/ml). Thus, 168 patients (75 per cent) had an AFP concentration in the range which is virtually diagnostic of HCC: 24 patients (10·7 per cent) had a value of 501–1000 ng/ml, 36 (16·1 per cent) 1001–10 000 ng/ml, 78 (34·8 per cent) 10 001–100 000 ng/ml, and 30 (13·4 per cent) greater than 100 000 ng/ml.

Hepatitis B virus status

HBsAg was positive in the serum of 161 patients (71·9 per cent) (current hepatitis B virus infection) and anti-HBc and/or anti-HBs in 59 patients (26·3 per cent) (past hepatitis B virus infection). Four patients (1·8 per cent) had no serum markers of current or past hepatitis B virus infection.

Cirrhosis

Because the presence or absence of cirrhosis in the non-tumorous portion of the liver can only be ascertained with certainty at necropsy (or laparotomy), comprehensive information concerning cirrhosis is not available in this group of patients. However, based on data obtained at necropsy on a large series of rural mine workers, cirrhosis is known to be present in 60 per cent of these patients[5]. The cirrhosis is almost invariably of the macronodular variety.

Discussion

There are several reasons for the very low resectability rate in the population we have studied. In the majority of the patients tumour grows extremely rapidly, with doubling times (based on serial serum AFP concentrations) which may be as short as 10 days[6]. As a result, the clinical course of the disease is usually fulminant, with an average survival time from the onset of symptoms of 11 weeks and from diagnosis of 6 weeks[5]. The tumour also reaches a considerable size: the average weight of the tumorous liver is 3914 g compared with 2036 g in Japanese patients and 2615 g in Western patients[7–9]. The tumour is often multinodular, and when of the massive variety, satellite nodules are frequently present[9]. Consequently, HCC is rarely confined to one hepatic lobe. Furthermore, the massive variety of HCC is rarely well-encapsulated.

HCC has a particular propensity to invade the portal venous and hepatic venous systems. Seventy per cent of patients in this population have tumorous infiltration of portal venous radicles at necropsy, and 14 per cent have invasion of the hepatic veins[7]. With the latter, the tumour plug not infrequently (9 per cent) grows into the inferior vena cava and may then grow into the right atrium (2 per cent)[7]. Tumour emboli originating from either the hepatic veins or the inferior vena cava travel via the right atrium to the lungs, resulting in the formation of multiple pulmonary metastases. Pulmonary metastases are detectable radiologically in 19 per cent at the time they are first seen and they appear in a further 6 per cent of patients during life[10]. Obstruction to either the portal venous or the hepatic venous system results in portal hypertension and ascites. If the patient survives long enough, oesophageal varices may develop and rupture.

Tumour rupture with consequent acute haemoperitoneum is not uncommon[7]. This complication carries an even graver prognosis than is usual for HCC. It is ironic that one of the two patients in the present series who proved to have a resectable tumour presented with an acute haemoperitoneum following tumour rupture. The explanation in this patient for rupture of a tumour small enough to be resected was that he was assaulted on the abdomen, causing rupture of a tumour that would presumably not otherwise have done so.

The fibrolamellar variant of HCC, which occurs not infrequently in Western patients and is more often amenable to resection than other histological types of the tumour[11], has not yet been reported to occur in the population studied.

The tumour may directly infiltrate adjacent structures, such as the diaphragm, or spread to regional lymph glands, the peritoneum, or elsewhere. Another factor to be considered is the coexistence of cirrhosis. Macronodular cirrhosis is present in 60 per cent of patients with HCC in this population. Even if the tumour is confined to the right hepatic lobe, resection is contra-indicated if the left lobe is cirrhotic because of the inevitability of postoperative hepatic failure. Resection of a left lobe tumour is feasible provided the cirrhosis of the right lobe is not advanced.

Because of the risk of disseminating the tumour along the needle track, into the peritoneal cavity, or into the blood stream, percutaneous biopsy was not undertaken as long as the HCC was thought to be resectable. However, a needle biopsy of the hepatic lobe believed to be free from tumour is useful in order to ascertain whether or not cirrhosis is present and, if present in the right lobe, how advanced the cirrhosis is.

During recent years the number of HCCs being successfully resected has increased. This is attributable to more careful patient selection, improved operative and anaesthetic techniques, and more expert postoperative management. Since the introduction of mass screening for early tumours with its higher yield of resectable lesions, tumours discovered in this way are being included in published analyses along with the advanced tumours, and this too has contributed to the higher operability rates.

In summary, the extremely low resectability rate as well as the dismal results obtained with conservative treatment reinforces the urgent need to detect these tumours at a stage when they are amenable to surgery. Surveillance programmes of individuals at high risk, such as chronic carriers from childhood of the hepatitis B virus, and patients with cirrhosis or haemochromatosis with a view to curative surgery (so-called secondary prevention) are being carried out in those populations in which this tumour occurs commonly, and encouraging results in terms of operability rates and 5-year survival rates are being reported[1]. However, in the long term it is mandatory to prevent this carcinoma. With the present-day evidence that the hepatitis B virus may be the initiator of 80 per cent of HCC worldwide, and the availability of effective and safe component vaccines against this virus, prevention of the great majority of these tumours could become a reality in the not too distant future.

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Parastomal hernia in relation to site of the abdominal stoma

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Parastomal hernia is a common late complication of enterostomy, especially colostomy, and sometimes requires surgical treatment. A possible contributory factor, location of the stoma in relation to the rectus abdominis muscle, was studied by examination of 130 patients with permanent intestinal stoma. The bowel had been brought out through the rectus abdominis muscle in 107 patients and lateral to it in 23 patients. The respective prevalence of parastomal hernia in these groups was 2·8 per cent and 21·6 per cent. The highly significant difference indicates that enterostomy should be constructed through the rectus abdominis muscle, not lateral to it.

Keywords: Parastomal hernia, enterostomy

Parastomal (or peristomal) hernia arises when there is a gap between the intestinal segment forming a stoma and the surrounding tissue. The bowel protrudes through the fascial defect and the result is bulging, circumferential or partial, at the base of the stoma. Parastomal hernia is the commonest late complication of enterostomy, but should be distinguished from subcutaneous prolapse. The protrusion is accentuated when the intra-abdominal pressure rises. It may appear only as a slight bulging when the patient coughs, or may be very large.

Stoma-associated hernia can be psychologically distressing, as it is sometimes difficult to conceal under clothing. It may also give rise to abdominal discomfort due to intermittent intestinal obstruction, or to difficulties with the collecting appliance. Patients who irrigate a stoma with associated hernia commonly report unpredictable or poor return. Strangulation of the contents of a parastomal hernia may occur and require bowel resection[1-3].

Apart from weakness of the abdominal wall, several technical details in construction of a stoma can contribute to development of a parastomal hernia. The risk of hernia usually is increased if the intestinal segment forming the stoma is brought out through the abdominal incision or if the opening in the abdominal wall is too large[4,5]. As with other incisional hernias, chronic cough, obesity and malnutrition can be contributory factors.

Information on the incidence of parastomal hernia varies. Some authors maintain that a minor degree of parastomal weakness is present in many patients with colostomy, but does not fulfil the criteria for true hernia and seldom requires surgical correction[6,7]. Reported incidence, however, often concerns only cases requiring surgical treatment, or those in which the hernia interferes with wearing of an appliance[8,9]. Incidences of about 20 per cent following colostomy, and 5–10 per cent after ileostomy[10], have been reported.

In one colostomy technique the sigmoid is brought out through the oblique abdominal muscles lateral to the rectus muscle[6]. Other authors argue that the bowel should emerge through the rectus abdominis muscle in order to avoid development of parastomal hernia[11-14].

To investigate the possible influence of stoma site in relation to the rectus abdominis muscle on the risk of parastomal hernia, we have performed a follow-up study of patients with permanent intestinal stoma.

Patients and methods

The study comprised 65 men and 65 women attending the stomatherapy service at our hospital. Patients whose general health was too poor to permit attendance at the clinic, e.g. with end-stage cancer or senility, were excluded. The patients' mean age (±s.d.) was 54·6 ± 16·3 (range 19–84) years. The follow-up time was 7·0 ± 6·7 (1–36) years. The sex distribution in the various age groups is shown in *Table 1*.

The site for stoma was marked pre-operatively. The operations were done by several senior surgeons. Cross incisions were used at stoma construction, no excision of tissue other than skin, and a 'two-finger' aperture (*circa* 3·5 cm) was created. No patient had an extraperitoneal stoma.

The follow-up examinations were performed by the surgeon and staff nurse at the stomatherapy service. The collecting appliance was removed and the patient was examined in both supine and standing position. A parastomal hernia was defined as a bulge restricted to that area and caused by protrusion of abdominal contents. Subcutaneous prolapse or general muscular weakness with bulging of the lower part of the abdomen were thus excluded from the definition.

The parameters registered at the follow-up review were the underlying disease, possible concurrent disorder(s), age at operation, sex, body weight, type of enterostomy, surgical technique with special reference to relationship between stoma site and rectus abdominis muscle, any previous operation for parastomal hernia and time from construction of the stoma to appearance of parastomal hernia.

Results

Parastomal hernia had previously been surgically treated in 4 of the 130 patients, and was found in 5 others at the follow-up examination. The mean age at operation of these 9 patients was 48·2 ± 13·6 years, i.e. they were approximately 8 years younger than patients in the total series. The overall prevalence of parastomal hernia was 6·9 per cent (6·2 per cent in men, 7·7 per cent in women). All of the nine hernias were observed within 2 years after creation of the stoma, but they were widely distributed among the age groups and seemed to be independent of the follow-up time (*Table 2*).

Table 3 shows that the prevalence of parastomal hernia when the intestine had been pulled through the belly of the rectus abdominis muscle was 3/107 (2·8 per cent). When the stoma was lateral to the rectus muscle the figures were 6/23 (26·1 per cent), a statistically significant difference ($P = 0{\cdot}0004$, χ^2 test).

The relationship to type of stoma is presented in *Table 4*. Parastomal hernia was more common in sigmoidostomy than in ileostomy (8·9 per cent *versus* 2·2 per cent), but the difference was not statistically significant.

The disorders that had necessitated enterostomy are listed in *Table 5*. Three of the patients with parastomal hernia had been operated on for rectal carcinoma and three for ulcerative colitis. Faecal incontinence or sigmoid diverticulitis were the reasons for stoma in the other patients with hernia.

Table 1 *Age and sex of patients at stoma construction*

Age (years)	Males	Females
19	–	1
20–29	4	7
30–39	8	8
40–49	7	12
50–59	12	11
60–69	21	17
70–79	11	8
80–84	2	1
Total	65	65

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Table 2 *Parastomal hernia in relation to age at operation and follow-up time*

Age (years)	No. of patients	Follow-up (years)	Parastomal hernia (*n*)
19	1	11·0	—
20–29	11	9·3 ± 6·6	1
30–39	16	11·8 ± 10·1	1
40–49	19	10·5 ± 7·6	2
50–59	23	6·8 ± 6·7	3
60–69	38	4·7 ± 3·8	2
70–79	19	3·5 ± 3·4	—
80–84	3	3·3 ± 0·6	—

Values are mean ± s.d.

Table 3 *Parastomal hernia in relation to location of stoma*

Stoma position in relation to rectus abdominis muscle	Parastomal hernia *n* (%)
Through muscle	3/107 (2·8)
Lateral to muscle	6/23 (26·1)

Table 4 *Parastomal hernia in relation to stoma type*

Permanent stoma	*n*	Parastomal hernia (*n*)
Sigmoidostomy	79	7
Ileostomy	45	1
Loop ileostomy	3	1
Transversostomy	2	
Loop transversostomy	1	
Total	130	9

Table 5 *Parastomal hernia in relation to underlying disease*

Diagnosis	*n*	Parastomal hernia (*n*)
Rectal carcinoma	54	3
Ulcerative colitis	28	3
Crohn's disease	22	—
Faecal incontinence	14	2
Gynaecological disease	6	—
Diverticulitis	3	1
Colon carcinoma	1	—
Anal carcinoma	1	—
Pseudo-obstruction	1	—

Discussion

The prevalence of parastomal hernia in the present investigation was 6·9 per cent, including hernias which did not require surgical treatment. The 8·9 per cent prevalence after sigmoidostomy accords with a recent report[15]. Other authors reported only 1 per cent parastomal herniation among 200 patients with colostomy, but the great majority of these patients had loop colostomy and, accordingly, the most common complication was prolapse of the stoma[16]. Among all our patients with ileostomy the prevalence of parastomal hernia was 4·2 per cent. In end ileostomy (excluding loop ileostomy), however, the figure was only 2·2 per cent, which agrees with the view that parastomal hernia is less common after ileostomy than after colostomy[10,14,17].

A possible cause of parastomal hernia is increased intra-abdominal pressure from disorders of the respiratory or urinary organs. Obvious predisposition was found in only one patient. This patient was obese and was receiving corticosteroid treatment for severe asthma. Like earlier investigators[5], we found that neither increasing age nor underlying disease influenced the risk of parastomal hernia.

All the hernias in this series appeared less than 2 years after construction of the stoma. Technical factors in stoma construction are most commonly believed to be the dominant aetiological factors. The possibility that an extraperitoneal colostomy reduces the risk of herniation has been questioned[6]. In addition to the earlier mentioned risk factor of too large an aperture in the abdominal wall, location of the stoma in relation to the laparotomy incision or the rectus abdominis muscle may play a part. The stoma can be sited in or lateral to the laparotomy incision, or through or lateral to the rectus muscle. It is now generally agreed that siting of stoma within the incision should be done only in very special circumstances.

A possible, though uncommon, disadvantage of stoma through the rectus abdominis muscle is that problems with the collecting appliance can arise if the site is too close to the laparotomy incision or the umbilicus. Furthermore, there may be a risk of disturbed venous flow due to compression by muscle fibres and of stomal oedema.

Although it is often stated that experience shows the risk of parastomal hernia to be less when the bowel is brought out through, and not lateral to, the rectus abdominis muscle, few supporting data have hitherto been published[11–14]. In one retrospective study[18], the incidence of parastomal hernia was 19 per cent when the stoma was lateral to the rectus abdominis muscle, but only 1 per cent when it was transmuscular; however in that study only 93 of the 140 patients with end-sigmoidostomy could be re-examined, the others having died.

Disadvantages of our study were that it was retrospective and that exit of the bowel was more common through the rectus abdominis muscle than lateral to it. The prevalence of parastomal hernia nevertheless differed significantly according to location of the stoma. Thus the risk of parastomal hernia was reduced approximately tenfold when the bowel was brought out through the rectus abdominis muscle (2·8 *versus* 26·1 per cent). Our study supports the view that, in construction of an intestinal stoma, the bowel should exit through the rectus muscle in order to diminish the risk of parastomal hernia.

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Case report

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Fulminant pseudomembranous colitis with left hemicolon and rectal sparing

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The diagnosis of pseudomembranous colitis is based upon sigmoidoscopic, bacteriological and toxicological parameters. Standard textbooks and publications emphasize the importance of diagnostic sigmoidoscopy[1,2]. We present a fatal case of fulminant pseudomembranous colitis with left-sided colonic and rectal sparing.

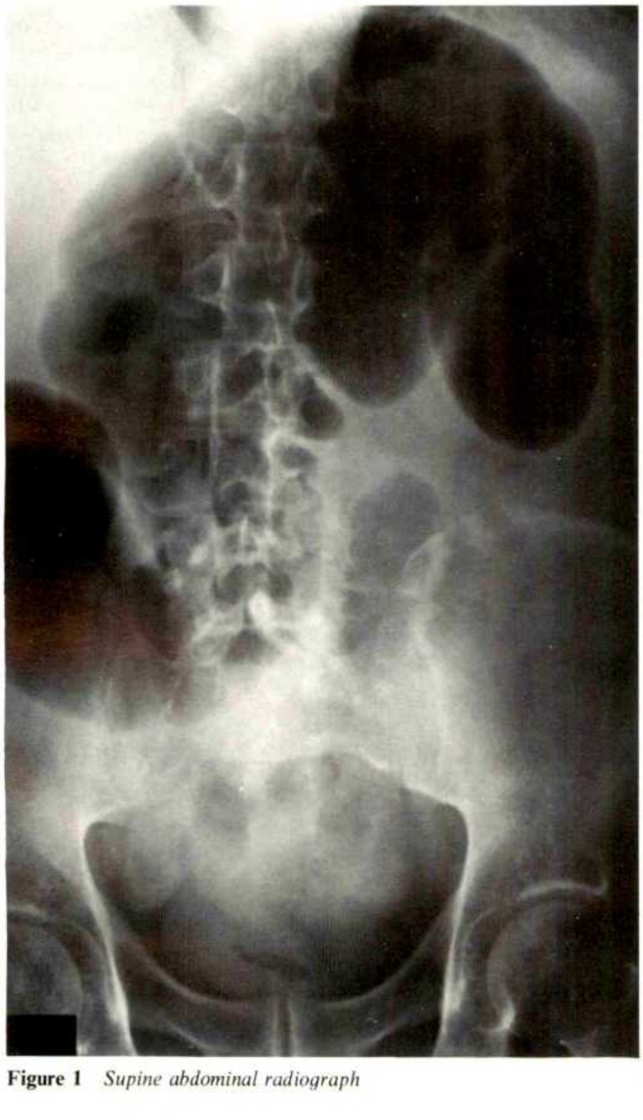

Figure 1 *Supine abdominal radiograph*

Case report

A 67-year-old asthmatic man underwent a right thoracotomy and surgical pleurodesis for recurrent pneumothoraces. Cefuroxime (Zinacef®, Glaxo Laboratories Ltd, UK) 750 mg IV was given preoperatively and continued for 2 days. Postoperatively his clinical course was complicated by a persistent pyrexia. On the 10th postoperative day he complained of abdominal distension, tenderness and passing a liquid stool. Investigation showed a neutrophil leucocytosis of $26\cdot1 \times 10^{9}$/l, and abdominal radiographs suggested large bowel obstruction at the level of the sigmoid colon (*Figure 1*). A presumptive diagnosis of pseudo-obstruction was made. No stenosing lesion was seen on flexible sigmoidoscopy to 60 cm, a finding confirmed by a limited barium enema to the splenic flexure which showed no abnormality. The patient continued to deteriorate and a decompressing caecostomy was performed. Despite this the patient died.

At autopsy the right half of the colon was found to be grossly dilated. The mucosa, from the caecum to the beginning of the transverse colon, was intensely congested and numerous scattered yellow plaques were present. The left side of the colon was of normal calibre and the mucosa appeared healthy. Histological examination showed the classic features of pseudomembranous colitis. The pseudomembranes, composed of a mixture of mucus, inflammatory exudate and necrotic debris, overlay groups of necrotic disrupted crypts. In the more severely affected areas there was confluent necrosis of the mucosa and degeneration of the muscle coats. Sections from the left side of the colon showed normal appearances. *Clostridium difficile* was isolated from the faeces and the test for the cytotoxin was positive.

Discussion

Pseudomembranous colitis is a well-recognized complication of cephalosporin administration. After major abdominal surgery the presentation can imitate common postoperative conditions, e.g. anastomotic dehiscence or pelvic abscess formation. Failure to recognize the diagnosis in these patients carries a high mortality rate[3]. Sigmoidoscopy has been advocated as the key investigation in order to visualize the pseudomembranes[4]. Latterly this has been used in conjunction with faecal toxin assays and stool cultures for *C. difficile*. However, pseudomembranous colitis with rectal sparing can occur and is well reported in the American literature[5]. Thus normal sigmoidoscopy and biopsy do not preclude the diagnosis.

We believe that if pseudomembranous colitis is suspected in postoperative patients then they should receive specific therapy with oral vancomycin or intravenous metronidazole, without awaiting bacteriological or toxicological confirmation. Failure to recognize this eminently treatable condition in the presence of normal sigmoidoscopy can prove fatal.

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Growth-promoting action of gastrin on human colonic and gastric tumour cells cultured in vitro

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The gastrointestinal hormone, gastrin, was examined for its trophic effect on the growth of colorectal and gastric tumour cells. All of the freshly disaggregated colorectal and gastric human adenocarcinomas responded to pentagastrin in 24 h cultures in vitro. *Two newly established adenocarcinoma cell lines showed a response to pentagastrin at passage 2 but not at passage 6. Long-established cell lines did not respond to pentagastrin; however, upon synchronization of the human gastric cell line, MKN45, a trophic growth response with gastrin-17 was observed. This response was enhanced when the same cell line was grown as a xenograft in nude mice and then examined* in vitro *for gastrin dependence; this dependence was gradually reduced on further* in vitro *passaging. These results indicate that trophic responses to gastrin are lost during* in vitro *culture and may be underestimated by using long-established tumour cell lines. However, as all of the early cultures of colorectal and gastric tumours respond trophically to gastrin, perhaps gastrin-receptor blockers may be an important therapeutic modality for these patients.*

Keywords: Gastrin, gastric cancer, colonic cancer

Endocrine control of cancer growth was first demonstrated in the 19th century by a Scottish surgeon[1] in a patient with breast carcinoma. It is well established that thyroid, prostatic and breast tumours are under hormonal control and that hormonal manipulation is an important therapeutic modality for these tumours[2–4]. Recently, interest has centred around the potential use of gastrointestinal peptides to regulate the growth of cancers of the digestive tract.

Gastrin is a trophic hormone for normal gastrointestinal tract epithelial cells[5,6] but more recently it has become clear that some gut tumour cells respond to gastrin, both *in vitro* and, at least in animals, *in vivo*[7–9]. The proportion of tumours in man which are sensitive to gastrin is not known.

Materials and methods

Freshly disaggregated human adenocarcinomas

Four human adenocarcinomas were aseptically disaggregated in 0·5 mg/ml collagenase (Boehringer-Mannheim) dissolved in Hanks' balanced salt solution (HBSS), for 20 min at 37°C, with stirring. The disaggregated cells were then filtered to remove large clumps, washed twice with HBSS and the effect of pentagastrin (250 μg/l) on cell growth was assessed by incorporation of ^{75}[Se]-selenomethionine (Amersham). For this, 5×10^3 cells/well were plated out in 96 well tissue culture plates (Flow Labs) in Dulbecco's growth medium (DMEM) supplemented with 10 per cent fetal calf serum (FCS). Pentagastrin was then added in 100 μl of culture medium and the cells were incubated for 64 h before the addition of 0·1 μCi of ^{75}[Se]-selenomethionine in 50 μl of culture medium. After 6 h incubation, both adherent cells and cells in suspension were separately assessed for ^{75}[Se]-selenomethionine uptake. Radioactivity was counted in a γ-counter.

Newly established human adenocarcinomas

Early cultures of one gastric (ST16) and two colorectal (C277, C280) adenocarcinomas were incubated with ^{75}[Se]-selenomethionine in the presence or absence of pentagastrin (250 μg/l). These experiments were performed at cell passage 2 and repeated at passage 6. The cells were proved to be 100 per cent epithelial in lineage at these passages by staining duplicate samples with an anticytokeratin monoclonal antibody as described[10] (data not shown).

Established cell lines

Established gastrointestinal cell lines were examined for gastrin dependence.

Seven colorectal (HCT8, HRT18, LoVo, HT29, C170, C168, LS174T) and one gastric cell line (MKN45) were maintained in DMEM and 10 per cent FCS and had been passaged over 500 times.

The effect of a range of pentagastrin concentrations (0–250 μg/l) and gastrin-17 (G-17, Sigma) concentrations (0–10 μg/l) on cell growth was assessed by incorporation of ^{75}[Se]-selenomethionine.

Cell doubling times were assessed by seeding flasks with 10^5 cells, allowing them to adhere for 2–4 h before adding pentagastrin (250 μg/l) or G-17 (10μg/l); control flasks were maintained without gastrin. The cells were then harvested at 24-h intervals and counted with the use of a haemocytometer.

Synchronization of selected cell cultures was achieved by the addition of excess thymidine, as described[11]. Cells were seeded into a 96-well plate at a concentration of 5×10^3/well and grown for 48 h in DMEM plus 10 per cent FCS and then a further 24 h in DMEM without FCS; finally, thymidine (2·0 mM) was added. After a further 24 h, the cells were pulsed with various concentrations of G-17 for an 8-h period; unsynchronized cells were included as the control. Cell growth was assessed by incorporation of ^{75}[Se]-selenomethionine and cell counting.

Synchronization was confirmed by staining the cells with 50 μg/ml propidium iodide (Sigma) and the DNA of individual cells was analysed by flow cytometry. DNA profiles with a single G_1 peak and no S-phase or G_2 peak were generated (data not shown).

Disaggregated xenograft cells from nude mice

The cell lines, LoVo, ST16 and MKN45 were grown as xenografts in Olac nude mice. For this, 2×10^7 cells were injected subcutaneously into the flanks of the selected animals and, after 3–5 weeks, tumour growth was evident. The tumours were aseptically dissected and disaggregated in collagenase as previously described for the human adenocarcinomas, and the resultant cell suspensions were maintained in culture *in vitro*.

After passage 2, the cells were synchronized as previously described and growth in the presence of G-17 was measured by ^{75}[Se]-selenomethionine incorporation.

All data were statistically analysed by the paired Student's *t* test and the term 'percentage of control', used to compare data, can be defined as:

$$\frac{\text{c.p.m. in presence of gastrin}}{\text{c.p.m. in absence of gastrin}}$$

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Results

Freshly disaggregated human adenocarcinomas

Enzyme disaggregation of solid tumours releases a mixed population of cells. Suspension cultures consisting of lymphocytes, red blood cells and epithelial clumps showed a significant response ($P < 0·01$) to pentagastrin in three out of four cultures. The adherent cells consisting of epithelial cells, macrophages and fibroblasts showed a comparatively reduced response to pentagastrin (*Table 1*).

Table 1 *Growth response of freshly disaggregated tumours in culture* in vitro *with and without pentagastrin (250 μg/l)*

	Uptake of ^{75}[Se]-selenomethionine (c p.m.)			
	Suspension cells		Adherent cells	
Tumour	Control	Pentagastrin	Control	Pentagastrin
Colorectal				
309	378±64	503±62	131±17	158±28
125	3648±676	20 699±1584	235±29	198±19
322	3291±66	4297±399	437±55	762±233
Gastric				
26	8856±2206	8018±2099	329±15	346±16

Values are mean±s.e m.

Table 2 *Effect of pentagastrin on growth of newly established human adenocarcinoma cell lines measured by ^{75}[Se]-selenomethionine incorporation*

Pentagastrin (μg/l)	Incorporation of ^{75}[Se]-selenomethionine (c.p.m.) in the tumour cell lines: ST16	C280	C277
0	737±78	2876±544	210±13
250 (passage 2)	1417±73	4714±944	309±22
0	7454±1253	6355±796	11 872±1163
250 (passage 6)	7590±920	5933±391	12 091±719

Values are mean±s e.m.

Newly established human adenocarcinomas

All three of the tumour cell lines responded to the addition of 250 μg/l pentagastrin at passage 2 by approximately a doubling in incorporation of ^{75}[Se]-selenomethionine, but no effect was seen when this was repeated at passage 6 (*Table 2*).

Established cell lines

The seven colorectal cell lines showed no response in growth rate to the addition of up to 250 μg/l of pentagastrin (*Table 3*) as measured by ^{75}[Se]-selenomethionine incorporation. MKN45, an established gastric cell line, and ST16 at passage 50 also showed no response to varying concentrations of pentagastrin (*Table 3*). Furthermore, LS174T and C170 did not respond to pentagastrin (doubling times 18 h and 15·5 h respectively) as measured by cell numbers over a 7-day experiment when compared with non-pentagastrin-treated controls (doubling times 20 h and 16 h respectively).

Synchronized cell lines

As pentagastrin failed to stimulate growth in established cell lines, the effect of the 17-amino-acid gastrin analogue G-17 was tested on synchronized and unsynchronized cells.

Unsynchronized MKN45 cells failed to respond to G-17 but corresponding synchronized cells showed a significant response to G-17 at 10 μg/l ($P < 0·05$). However LoVo and ST16 did not respond to G-17 with or without synchronization (*Table 4*).

Table 3 *Effect of pentagastrin on ^{75}[Se]-selenomethionine incorporation*

	Uptake of ^{75}[Se]-selenomethionine (c p.m.) at the following doses of pentagastrin (μg/l):								
Cell lines	0	1·5	3	15	25	125	150	250	1500
Colorectal									
HCT8	14 170±413	ND	11 211±225	ND	11 914±1086	9325±444	ND	11 197±829	ND
HRT18	9154±437	ND	7240±624	ND	6229±299	7004±1253	ND	8386±725	ND
LoVo	8796±504	ND	5640±668	ND	5612±304	5834±504	ND	5737±446	ND
HT29	5089±150	ND	3754±434	ND	3761±275	3689±73	ND	3946±485	ND
LS174T	9322±978	ND	10 843±266	ND	10 969±388	ND	ND	11 114±372	ND
C170	4062±87	ND	4344±243	ND	4565±402	ND	ND	4833±188	ND
C168	2060±49	ND	2394±213	ND	2206±297	ND	ND	2134±184	ND
Gastric									
MKN45	6970±397	6192±110	ND	5831±321	ND	ND	6536±1525	ND	7099±601
ST16	11 927±328	10 561±601	ND	10 330±283	ND	ND	10 281±475	ND	10 641±463

Values are mean±s.e.m. ND, not done

Table 4 *Growth response of gastric and colorectal cell lines to gastrin (G-17)*

	Uptake of ^{75}[Se]-selenomethionine (c.p.m) at the following doses of G-17 (μg/l):									
	Unsynchronized					Synchronized				
Cell line	0	0 2	1·0	2·0	10·0	0	0·2	1·0	2 0	10·0
MKN45	11 480±350	11 798±235	11 300±695	11 390±530	12 700±500	9980±290	10 120±385	9990±990	11 160±400	11 390±430*
ST16	2920±495	3130±280	3590±310	3560±320	3080±230	2900±98	2665±198	3050±110	2996±320	2690±165
LoVo	11 890±80	12 570±310	12 840±195	12 710±110	12 065±65	9198±165	9444±325	9620±378	8998±198	—

Values are mean±s.e.m. * $P < 0·05$

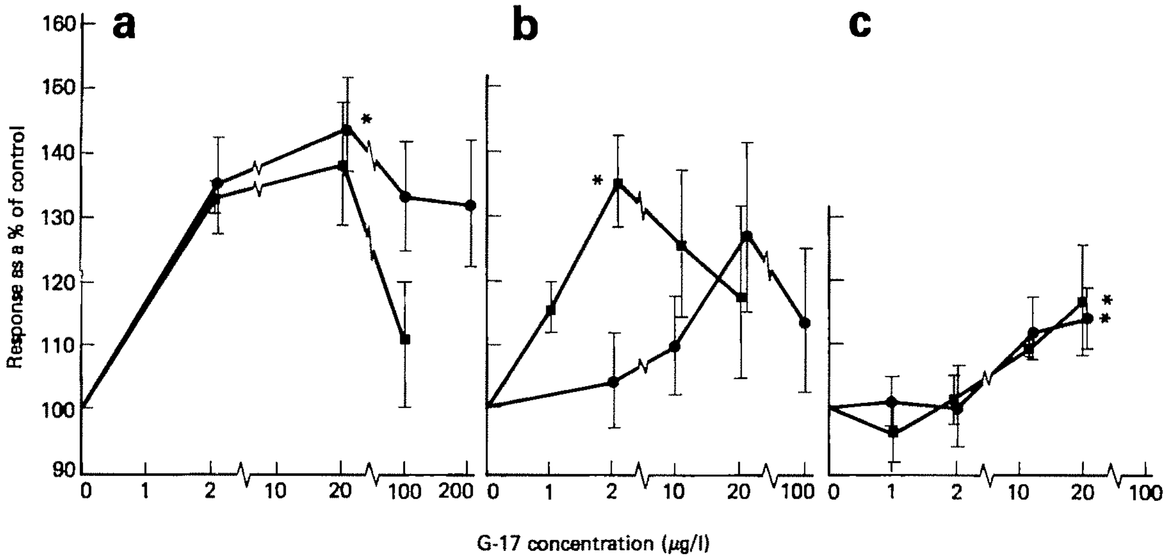

Figure 1 *The growth response of synchronized MKN45 cell cultures to G-17* **a**, *Xenograft cells, passage 2* ● *and 3* ■ *(single experiments)* (*$P<0.001$) **b**, *xenograft cells, passage 15* ■ *and 16* ● *(single experiments)* (*$P<0.01$), **c**, *>500 passages* ● ■ *(two separate experiments)* (*$P<0.10$)

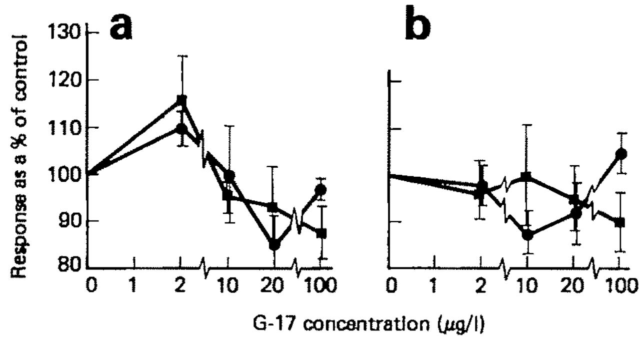

Figure 2 *The growth response of synchronized ST16 cell cultures to G-17.* **a**, *Xenograft cells, passage 2* ■ *and 3* ● *(single experiments),* **b**, *>500 passages* ● ■ *(two separate experiments)*

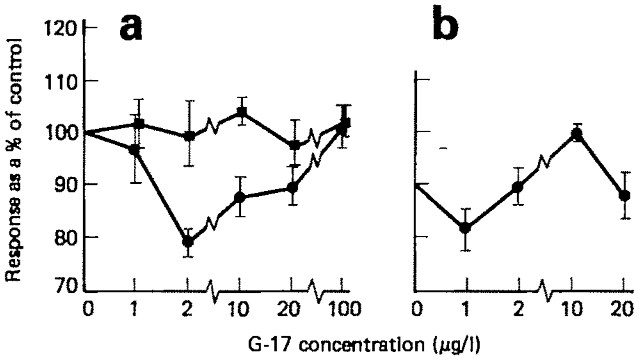

Figure 3 *The growth response of synchronized LoVo cell cultures to G-17.* **a**, *Xenograft cells, passage 2* ■ *and 3* ● *(single experiments);* **b**, *>500 passages* ● *(single experiments)*

These results were confirmed by measuring doubling times and total cell numbers. Synchronized MKN45 cells had a faster growth rate (21·6 h) and reached higher total numbers ($5{\cdot}95 \times 10^6$) when incubated in the presence of 10 μg/l G-17 than did synchronized but non-gastrin-treated cells (doubling time 36 h; total cell number, $3{\cdot}5 \times 10^6$).

Disaggregated xenograft cells from nude mice

Xenografts generated in mice by injection of LoVo, ST16 and MKN45 cell lines were isolated, disaggregated and assayed *in vitro* for gastrin dependence following thymidine synchronization. MKN45 xenograft cells showed a statistically significant ($P<0{\cdot}001$) trophic response to G-17 *in vitro* at passages 2 and 3. By cell passage 15 and 16 *in vitro*, this response had diminished and was less significant ($P<0{\cdot}01$) but the growth stimulation was greater than that seen with established MKN45 cells (*Figure 1*).

Synchronized ST16 and LoVo xenograft cells did not respond to G-17 at passages 2 and 3 at any of the doses examined (*Figures 2* and *3*).

Discussion

The three colorectal human tumours studied after disaggregation and 24 h culture *in vitro* responded to pentagastrin; however, the one gastric tumour did not. Cells in suspension produced a greater response, perhaps reflecting the greater number of epithelial cells in these cultures or possible interactions with lymphocytes. These results were similar to those of Sirinek and co-workers[12] who found that four out of four of their early cultured tumours were sensitive to gastrin. Rae-Venter *et al.*[13] demonstrated the presence of gastrin receptors in seven out of eight tumours studied.

Interestingly, two human adenocarcinomas still responded to gastrin after two passages in culture *in vitro*. These cells were 100 per cent epithelial in lineage, suggesting that other host cells were not responsible for the trophic effect seen in the first 24 h. However, by passage 6 of *in vitro* culture, these cell lines no longer responded to exogenous gastrin. The growth rate of both cell lines increased between passages 2 and 6, indicating that they were adapting to survive with the nutrients provided. As gastrin was not one of these nutrients they probably adapted to grow in its absence. Similarly, established cell lines failed to respond to pentagastrin or G-17 gastrin. However, after synchronization (which allows a more sensitive measurement of any stimulation) a modest response to G-17 could be detected in at least one cell line, MKN45. This response was enhanced after growth of these cells in nude mice, suggesting their growth *in vivo* is more gastrin dependent and this dependence is not immediately lost in subsequent early culture *in vitro* However loss in sensitivity to gastrin was gradually observed when xenograft-derived cells were continuously passed *in vitro*.

Kusyk's group have also demonstrated a trophic effect of gastrin on a colorectal cell line after cell synchronization and suggested that the cells were sensitive to this hormone only during the S-phase of cell growth[11]. The hormone gastrin clearly has some control over the growth of human gastric and colorectal tumours *in vitro* and *in vivo*. Although gastrin is probably the most studied of gastrointestinal peptides, other hormones may influence the growth of tumour cells associated with the gut and these include glucagon, secretin, cholecystokinin, cerulin and bombesin[14].

Receptor-blocking agents for some of these hormones are already available and others are under development. A recent report[15] citing the use of the relatively weak gastrin receptor blocking agent, proglumide, showed a reduction in the growth of a mouse colonic adenocarcinoma. Gastrin-receptor blockers may well be an important therapeutic modality for patients with both gastric and colorectal carcinomas.

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Description of drugs and materials

The Journal is encountering increasing problems in ensuring the correct description of drugs and materials. Whenever possible, authors are encouraged to use the generic name and to avoid using the trade name for the materials in question. If a specific product manufactured by a particular company is to be preferred, then this should be made absolutely clear.

Review

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Bacterial short-chain fatty acids and mucosal diseases of the colon

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This review examines the potential association between short-chain fatty acids and mucosal diseases of the colon, and discusses the implication of these relationships and the surgical management of large bowel disorders.

Keywords: Colonic disease, short chain fatty acids

The morbidity and mortality of colonic diseases continue to pose prominent problems in Western society. Diseases of neuromuscular origin—diverticulosis, chronic constipation, irritable colon syndrome and pseudo-obstruction—are separable from those of predominantly mucosal origin—polyps, carcinoma, ulcerative colitis and other forms of colitis. The mucosally associated diseases have recently been linked with bacterial metabolites of fermentable fibre, mainly short-chain fatty acids (SCFAs): namely acetate, propionate and butyrate[1]. This brief review elucidates the potential associations between short chain fatty acids, mucosal diseases and surgical options in the management of colonic diseases.

Colonocyte turnover and anastomotic healing

Epithelial cells of the colonic mucosa (colonocytes) derive most of their energy supply (60–70 per cent) from the colonic lumen and the distal colon is more dependent on luminal nutrition by SCFAs, in contradistinction to vascular nutrition, than either the proximal colon or small intestine[2]. Mucosal growth, of which crypt-cell production rate is a major index, depends upon luminal nutrition, availability of growth factors and neuronal control mechanisms. With regard to luminal nutrition, both crypt-cell production rate[3] and mucosal weight of the colon[4] are decreased by the absence of SCFAs or by diminished production of SCFAs because of the unavailability of fermentable dietary fibre. Anastomoses in the distal colon are less likely to disrupt spontaneously or to burst if the luminal SCFAs are plentiful than when they are absent[5]. This suggests that SCFAs may accelerate mucosal healing, although other sources for mucosal nutrition have not yet been tested. The accelerated healing of experimental anastomoses with SCFAs need not be due solely to stimulation of mucosal cell proliferation but could also be due to enhanced blood flow to the colon, an effect known to occur with sodium acetate[6]. With these reservations in mind, clinical inferences have been drawn from the experiments that SCFAs in the colonic lumen may strengthen anastomoses or accelerate anastomotic healing, particularly in cases where the distal colon has been defunctioned and where SCFAs are not readily available. A means of instilling such fatty acids into the defunctioned colon could conceivably prove to be of benefit to mucosal healing in man, but to date this has not been put to the experimental test.

Non-resectional postoperative diarrhoea

Loose bowel motions after abdominal operations are commonly observed. One of many explanations for the observation could be removal of SCFAs from the colonic lumen, a factor which markedly reduces the absorptive capacity of the colonic mucosa[7,8]. Tilson *et al.*[9] were the first to show a reduced capacity of sodium absorption in the colon that had been defunctioned. Subsequent investigations[10,11] demonstrated that the efficiency of sodium absorption in the defunctioned colon and the capacity of the colon to salvage sodium depended upon the presence of bacterial fatty acids in the colonic lumen. These acids exert a trophic effect on the mucosa[7,8] in the sense that there are no obvious histological changes but a marked decrease in the mucosal activity of enzymes of fatty acid oxidation when fatty acids are removed from the colonic lumen. Re-exposure of the defunctioned colon to SCFAs partially redresses the imbalances of sodium absorption[7] although these experiments only assessed a short interval of re-exposure to bacterial fatty acids and did not take into consideration the loss of other bacterial metabolites. A large proportion of postoperative diarrhoea could be due to the degree and length over which the fermentative bacteria and thus SCFAs and bacterial metabolites are pre-operatively removed from the colon. Lengthy pre-operative bowel preparations or diminished luminal nutrition are probable determinants in the development of postoperative malabsorption although this has not been directly studied in the postoperative state. A means of restoring colonic absorption would be to encourage intake of fermentable substrate to produce SCFAs. Such a remedy has also been suggested to combat the diarrhoea of chronic starvation[12].

Post-resectional colonic diarrhoea

Removal of more than 100 cm of terminal ileum together with the ascending colon will produce troublesome diarrhoea in many patients[13,14]. While excess long-chain fatty acid[15] and bile salts entering the colon have been offered as an explanation for the subsequent diarrhoea[14], further experimental evidence indicates that SCFAs protect against the impaired absorption of sodium induced by bile salts in the ascending colon and that this protection is lost when the ascending colon is removed[16]. A protective effect of SCFAs is not observed in the descending

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Table 1 *Outcome following limited colectomy for ulcerative colitis*

Reference	Limited L-sided resection (No.)	Disease free (No.)	Recurrent disease: No surgery (No.)	Recurrent disease: Surgery (No.)	Observation time
Stahlgren *et al.*[30] (1959)	19	7	—	12	10–22 years
Hughes and Bennett[31] (1972)	6	5	—	1 (stricture)	+10 years
Roediger *et al*[32] (1982)					
Webster and Howard[33] (1973)	2	2	—	—	6+8 years
Clark and Ward[34] (1980)	4	0	3	1	6 months–2 years
Johnston *et al.*[35] (1981)	6	0	1	5	12–17 months
Nakano *et al.*[36] (1984)	4	2	2	0	5–13 years
Roediger (unpublished) (1987)	2	0	1	1	6+12 months
Total	43	16	7	20	

colon. Preservation of the ascending colon would therefore be desirable to retain mucosal surface upon which SCFAs can exert a protective effect against the cathartic action of unabsorbed bile salts in the distal colon.

Colonic polyps and carcinoma

Analyses of anatomical distribution have shown that colonic polyps are found more frequently in the descending colon and rectosigmoid region than other parts of the colon[17,18]. Distributional studies, biochemical studies of colonocytes[2] and studies of colonic carcinoma have found a common ground in the action of SCFAs on the colonic epithelium. Butyrate makes the greatest regional contribution to epithelial nutrition in the distal colon[2] where the largest proportion of polyps are found[17,18]. Butyrate also has a differentiating effect on human carcinomatous cells grown *in vitro*[19] and, furthermore, increases the development of colonic tumours induced by dimethyl hydrazine *in vivo*[20,21]. Juxtaposing such findings—tumour siting, dependence of epithelial cells at the tumour site on butyrate and the influence of butyrate on growth characteristics of colonic tumours—provides a link between the neoplastic activity and normal nutrition of colonic epithelial cells. The type of change of the growth characteristics brought about by butyrate in colonic tumours is currently unsettled as both tumour proliferation and growth inhibition have been observed with butyrate in colonic tumours[19,20]. Observations on the effect of butyrate on the growth of other epithelial tumours have been associated with observed changes in enzyme activity or histone structure of tumour cells[22]. The interaction of nucleic acid metabolism, fatty acid metabolism and tumour growth in the distal colon clearly requires more effective study and should prove a worthwhile field of enquiry in the future.

Ulcerative colitis and fatty acid metabolism

The development of ulcerative colitis has been linked to inhibition of fatty acid oxidation in colonic epithelial cells, an observation made both *in vitro*[23] and *in vivo*[24]. Two types of experimental colitis based upon inhibition of enzymes of fatty acid oxidation[25] or reduced activation of fatty acids for oxidation[26] resulted in mucosal lesions closely resembling ulcerative colitis in man. This, and collateral evidence from other lines of research[27,28], has led to the metabolic hypothesis of causation of ulcerative colitis wherein impaired oxidation of fatty acids in colonocytes is postulated to be a primary event in the disease process[29]. One advantage of the metabolic hypothesis of ulcerative colitis is that it explains the distribution of disease along the length of the colon. Commencement of the disease at the rectum and progression proximally is in line with the importance of fatty acid oxidation to mucosal integrity and presumably is one factor controlling the proximal progression of the disease. The differential distribution of the disease along the length of the colon, in particular severe left-sided colitis, has led to the practice of limited colonic resections[30–36] with preservation of the proximal colon to facilitate absorption (*Table 1*). Despite clinical experience which indicates that the entire colon may eventually succumb to colitis, limited resections have, never the less, been undertaken.

Only 37 per cent of the cases treated with limited resections for left-sided colitis have remained disease free over varying intervals of follow-up (*Table 1*). Limited colonic resection cannot be advocated at present until further information concerning inhibition of fatty acid oxidation and factors governing the proximal spread of the disease are known.

Diversion colitis

Diversion colitis was reported for the first time in 1981 and has since then been studied by histological[37,38], radiological[39] and immunological means[40]. The condition is marked by non-specific inflammatory changes in cases where the faecal stream has been diverted, especially from the distal colon. Restoring the faecal stream leads to resolution of the inflammatory changes. The pathogenesis of the disease is unknown but a proposed explanation is that diversion colitis may represent an extreme form of nutritional deficiency of the colonic mucosa[38] which, in conjunction with a specific microbiological environment, leads to this type of colitis. Clinical studies to test the nutritional hypothesis and the role of short-chain fatty acids in this rare form of colitis have now been undertaken in a few cases. A preliminary report indicates that irrigation of the defunctioned colon with SCFAs led to histological resolution of diversion colitis, whereas irrigation with saline failed to resolve the colitis[41]. Manifestation of diversion colitis could therefore be due to a lack of luminal nutrition of the colonic mucosa and be resolvable by restoring the faecal stream Further detailed observations of this condition are required to prove a nutritional basis as the cause for this form of colitis. A similar mucosal disease due to lack of luminal SCFAs and resolvable by administering SCFAs has been observed in another fermentative organ, the rumen of cattle and sheep[42].

In conclusion the perspective on diseases of the colonic mucosa has changed with evidence that bacterial metabolites may influence both the function and growth potential of colonic epithelial cells. The variety of luminal metabolites now known and the various manipulations brought about by surgery of the gastrointestinal tract provide a unique opportunity to obtain new knowledge of the pathogenesis of mucosally associated diseases of the colon and may prove to have important implications for treatment.

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The pulsed dye laser and atherosclerotic vascular disease

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The use of a pulsed dye laser to ablate atheromatous tissue obtained from post-mortem human aortic specimens is reported. Laser energy was delivered with a 600 μm quartz fibre, at a wavelength of 504 nm and a pulse length of 1 μs. Pulse energy was varied from 30–140 mJ, producing peak pulse powers of the order of 100 kW. With these parameters the laser ablated fatty, fibrous and calcified plaques. At this wavelength atheroma is vaporized but there is minimal damage to normal vessel wall, due to preferential absorption of the laser light. Light microscopy shows that by microsecond pulsing, thermal damage to surrounding tissues associated with continuous wave lasers is avoided. Transmission electron micrographs reveal a sharp demarcation between a laser crater and the adjacent vessel wall with little ultrastructural disruption. Scanning electron micrographs show the crater walls to be smooth. The pulsed dye laser may therefore be effective in the treatment of occlusive peripheral vascular disease without undue risk of vessel perforation.

Keywords: Laser, laser surgery, arteriosclerosis

The use of a laser for the treatment of arterial disease was proposed by McGuff *et al.* in 1963[1], only 4 years after successful production of the first laser by Maiman[2] at the Howard Hughes Research Laboratories. With the development of flexible fibreoptic light guides that can be manipulated within arteries, two medical lasers, the argon and neodymium YAG devices, have been explored in animal models and their use has recently been reported in human peripheral arteries[3,4]. Conversion of the light energy in the laser beam into heat in the target tissue raises the temperature sufficiently to produce coagulation and then vaporization of atheroma. There is considerable debate as to the most efficient and safe laser parameters in terms of power, wavelength and energy delivery. Prince *et al.*[5] have demonstrated by spectroscopic analysis that atheroma preferentially absorbs wavelengths at the blue/green end of the visible spectrum and Deckelbaum *et al.*[6] have shown that damage to the surrounding tissues by conducted heat can be minimized by pulsing the laser light. In this study we report the use of a pulsed dye laser applied to cardiovascular disease *in vitro*, taking advantage of both preferential absorption and the benefits of pulsing.

Material and methods

A pulsed dye laser (Candela Corporation, USA) was used, in which the active medium was a 1×10^{-4} M solution of the organic dye coumarin 504 dissolved in equal proportions of methanol and water. This produces a beam with a wavelength of 504 nm at the blue–green end of the visible spectrum. One-microsecond pulses were produced at a rate of 10 pulses per second. The laser beam was focused onto the polished end of a 600 μm diameter flexible quartz fibre (Pilkington Medical). Pulse energy could be varied from 30 to 140 mJ, equivalent to an energy density of 10–50 J/cm^2. At 100 mJ a peak pulse power of 100 kW is produced at a peak power density of the order of 4 MW/cm^2. Twelve fresh human cadaver aortas were cut into 1 cm^2 samples and divided macroscopically into two groups: those that appeared normal and those that were atheromatous. The latter group included yellow fatty, white fibrous and frankly calcified plaques. Laser pulses were conveyed to each sample in turn via the optical fibre which was held perpendicularly to and in direct contact with the specimen by a counterbalanced arm. Craters were produced using a range of pulse energies (30–140 mJ). The power output at the fibre tip was measured using a Coherent 210 power meter (Coherent Components Group, California, USA) before and after each exposure. The duration of each exposure was accurately timed using an external trigger device to activate the laser for periods of exactly 5, 10, 15 and 20 s. Samples were immediately snap-frozen in a CO_2-ice/isopentane mixture and then stored at −80°C.

After mounting in Cryo-M-Bed (Bright Instrument Co. Ltd), craters were cut longitudinally on a cryotome into 30 μm sections, mounted and then air-dried on glass slides. Crater depths were measured by optical micrometry using a Leitz Dialux 22 Binocular microscope and a calibrated eyepiece graticule (Graticules Ltd). After measurement the craters were fixed in 10 per cent formaldehyde solution, stained with haematoxylin and eosin and examined by light microscopy to assess the degree of atheromatous change and to detect any signs of thermal damage to the surrounding tissue. Craters from both the normal and the atheromatous groups were prepared for electron microscopy by fixation in 0·1 M cacodylate-buffered 3 per cent glutaraldehyde. After dehydration in alcohols, six specimens were critical-point dried, coated with gold and examined with a Jeol-JSM-35CF scanning electron microscope to observe the details of the crater surface contour. A further six samples were fixed in osmium tetroxide and examined with a Jeol 100SX transmission electron microscope to assess the degree of cellular and subcellular damage in the tissues immediately adjacent to the crater edge.

Discussion

A total of 596 craters were made at pulse energies from 30–140 mJ in increments of 10 mJ. At each energy level six craters were made in normal and atherosclerotic specimens at exposure times of 5, 10, 15 and 20 s. There was no significant macroscopic or microscopic evidence of crater production using pulse energies of less than 40 mJ. Pulse energies in excess of 60 mJ led to increasingly frequent wall perforations and disruption also occurred in a radial direction along planes between and within the intima and media.

Crater depth measurement

The depth of craters increased in both macroscopically normal and atheromatous samples with increasing energy. At corresponding energy levels the crater depth in atheromatous samples was significantly greater than that in normal aortic wall. The median and range of the crater depths produced at the 50 mJ energy level are presented in *Figure 1* ($P < 0·01$ at each energy level, Mann–Whitney *U* test).

Light microscopy

Light microscopic findings after haematoxylin and eosin staining were similar in all specimens, comprising a symmetrical crater at the edge of which was a discontinuous linear basophilia 20 μm in width (*Figure 2*). The histological appearances of continuous wave lasing, namely charring, coagulation necrosis and cystic spaces, known as polymorphous lacunae, were not

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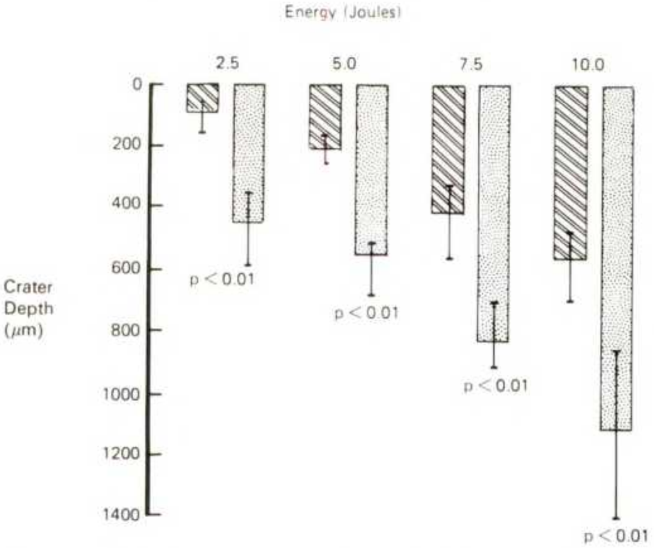

Figure 1 *The relationship between increasing total energy and crater depth. All craters made at a pulse energy of 50 mJ; six craters at each data point.* ▨, *Normal aortic wall;* ░, *atheromatous aortic wall; Mann–Whitney* U *test*

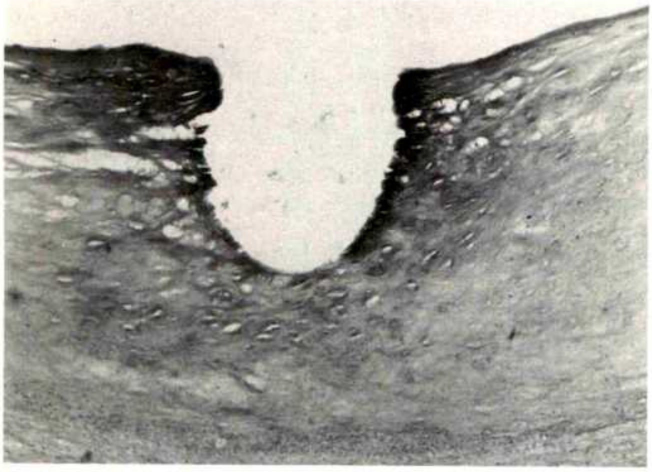

Figure 2 *Photomicrograph of a crater in an atheromatous plaque produced with a pulse energy of 50 mJ for 100 pulses (total energy 5 J), to show lack of adjacent thermal damage (magnification × 20)*

seen in craters produced with the pulsed dye laser. These features are demonstrated in *Figure 3*, this crater having been produced using a continuous-wave argon laser, at a power of 8W for 10 s.

Craters were produced over the whole range of atheromatous tissue, from simple yellow fatty plaques to complex fibro-fatty and calcified plaques.

Electron microscopy

Scanning electron microscopy revealed craters with a smooth wall and base (*Figure 4*). Charred particulate matter was not seen and irregular disruption of the wall was only found at pulse energies in excess of 60 mJ.

Transmission electron microscopy revealed a narrow zone of cellular disruption 20 μm in thickness at the crater–tissue interface.

Discussion

The effect of a laser on human tissue depends upon the specific absorption of the wavelength of light employed and on the mode of delivery of this energy. Lasers can be harnessed to produce purely thermal effects, e.g. using an argon laser to heat a metal tip mounted on an optical fibre. This system has been used to recanalize occluded femoral and coronary vessels[7,8]. However, lasers will have a more sophisticated role in the treatment of arterial disease if they can be used to specifically remove atheroma without causing unwanted damage to the structure of the vessel.

In the pulsed laser system that we have used in this study, trains of pulses in which the individual pulse energy was less than 40 mJ had no consistently measurable effect on either normal or atheromatous arterial wall. Pulse energies greater than 60 mJ produced craters with irregular splitting along planes within the intima and media, reflecting the dissipation of energy as a mechanical force and not just as a thermal event. Optimal effects were produced at 50 mJ per pulse where crater depth was found to be significantly greater in atheromatous than normal aortic wall. This finding is in agreement with work by Prince *et al.*[5] who, using absorption spectroscopy, reported that atheromatous vessel wall absorbs wavelengths of the order of 500 nm to a greater extent than does normal arterial wall. In the experiments reported in this paper the laser fibre was held at right angles to the vessel wall. Lasing *in vivo* will take place along the axis of the vessel and while an equivalent level of atheroma ablation should be achieved, pulse energies of the order of 50 mJ will have a minimal risk of wall perforation.

With increasing total energy and crater depth the selectivity in favour of atheroma appears to decrease (*Figure 1*). Light

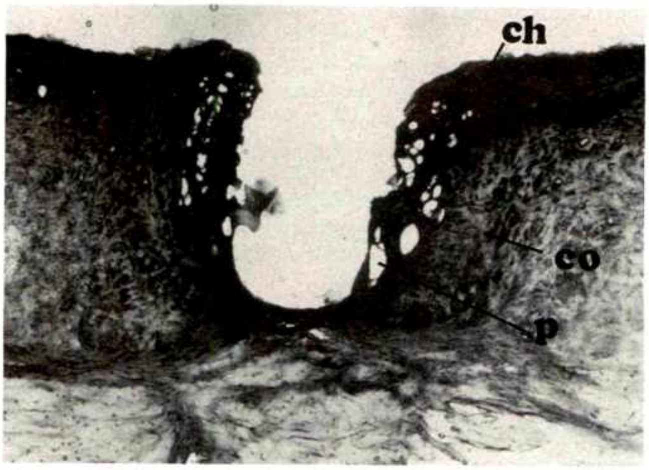

Figure 3 *Photomicrograph of a crater produced using a continuous wave argon laser (8 W for 10 s), showing charring (ch), coagulation (co) and polymorphous lacunae (p) (magnification × 20)*

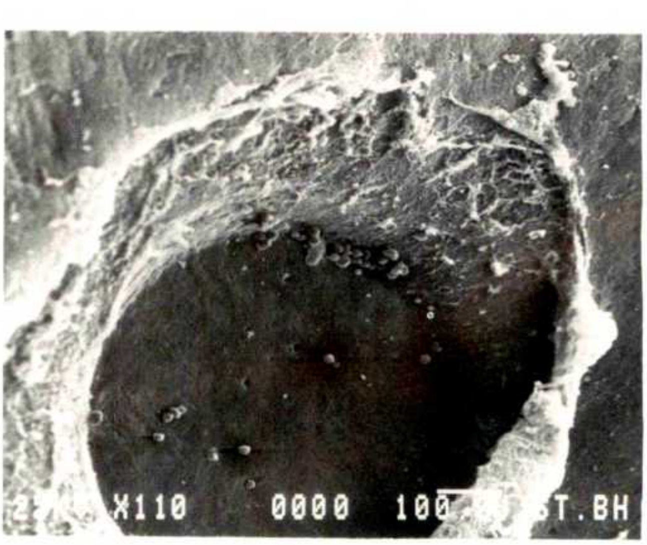

Figure 4 *Scanning electron micrograph of a crater in an atheromatous plaque revealing a smooth wall and base (magnification × 90)*

microscopy suggests that this is due to the ablative path reaching the medial layer of the arterial wall. One would not expect large differences between the absorptive patterns of normal and atheromatous specimens here, since atheroma is predominantly an intimal disease, and the media, although thinned, is relatively normal.

Light microscopy confirms the absence of the typical histological appearances of coagulation and charring found with continuous rather than pulsed lasing. This factor will also help to minimize the risk of perforation. Craters were smooth-walled on electron microscopy, a feature that is likely to improve flow characteristics and lead to more rapid healing and re-endothelialization *in vivo*, which in turn may decrease early failure due to thrombosis. The lack of damage beyond the crater wall is consistent with the theories regarding laser–tissue interaction when using pulsed energy. If the pulse length is short enough and the interval between pulses long enough, there is a finite time for any heat remaining after the initial vaporization to diffuse away through surrounding tissues. This period is designated as the 'thermal relaxation time' and its magnitude depends upon the volume, specific heat and thermal conductivity of the ablated tissue. The use of this parameter in determining and understanding the effects of lasers on tissues has been reported by Parrish *et al.*[9].

The controlled ablation which can occur when using pulsed radiation was initially described by Isner *et al.*[10] using excimer lasers which produce beams of ultraviolet light. There have been some fundamental problems concerning the conduction of these very short wavelengths in fibreoptics, which are only now being overcome. There remains the theoretical risk of mutagenicity related to the ultraviolet wavelengths and this may yet limit the application of these devices. The microsecond-pulsed dye laser overcomes both of these disadvantages.

Continuous wave lasers have difficulty in ablating calcified atheroma since the melting point of the calcium salts is of the order of 2000°C. Microsecond-pulsed lasers were initially developed in medicine for the destruction of urinary stones[11]. This is achieved by the production of shock waves at the interface between the fibre tip and the stone. The waves are then propagated through the stone causing fragmentation. This process enables the pulsed dye laser to disrupt the heavily calcified plaques present in some vessels that are resistant to the purely thermal effects of laser energy.

In summary, the pulsed dye laser offers the advantages of good conduction in fibreoptics, precisely controlled ablation without adjacent thermal damage, preferential absorption by atheroma, and the ability to disrupt calcified tissues. All these benefits are highly desirable when contemplating the use of laser energy for the treatment of human peripheral vascular disease.

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The American Journal of Surgery

Starting this month the Editors of *The British Journal of Surgery* are pleased to announce that for a trial period we will publish monthly the contents list of *The American Journal of Surgery*. The contents list of the March issue of *The American Journal of Surgery* can be found on the inside back cover of this issue.

Br. J. Surg. 1988, Vol 75, April, 352–356

Venous reflux: quantification and correlation with the clinical severity of chronic venous disease

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Air-plethysmography has been used to measure, in ml and in ml 100 ml^{-1} of tissue, the blood volume that filled the leg veins on changing posture from the recumbent position to standing. The venous filling index (VFI) (average filling range) was measured in ml s^{-1} and in ml 100 ml^{-1} min^{-1}. We studied 24 normal legs (N), 21 with primary varicose veins without chronic swelling, skin changes (liposclerosis, eczema, pigmentation) or ulceration (PVV) and 59 with chronic swelling and/or skin changes and/or ulceration; of these 59 legs, 31 had primary varicose veins (PVV/S) and 28 had popliteal reflux (PR). The classification was done according to clinical examination, Duplex scanning, ambulatory venous pressure measurements and venography. There was an increased incidence of sequelae with increasing values of VFI. The incidence of these sequelae was irrespective of whether reflux was in the deep or in the superficial veins. VFI is a practical non-invasive measurement of reflux. It should be used to study the effect of therapy and particularly to evaluate new reconstructive procedures designed to abolish reflux in the deep veins.

Keywords: Venous reflux, air plethysmography, venous ulcer

Incompetence of venous valves producing venous reflux is one of the major causes of chronic venous disease[1]. However, the minimum amount of reflux that can produce symptoms is not known.

Operations aiming to abolish reflux in the superficial system are well established, but it is not so with operations for the deep system. Valvuloplasty[2], venous transposition[3] and valve autotransplantation[4–6] are relatively recent procedures, and are still considered to be at the experimental stage. The selection of patients for and the evaluation of the results of these operations, so far, have been based mainly on venography and photoplethysmography[3,6] although some authors have included ambulatory venous pressure measurements[6]. Venography and ambulatory venous pressure measurements are invasive and give only indirect information about the amount of venous reflux. Photoplethysmographic measurements, though non-invasive, provide limited information on the amount of reflux for patients with ambulatory venous pressures over 40 mmHg[7], which happens to be the group with the more severe venous disease[1].

The aim of our study was to measure venous reflux and to correlate the amount of reflux with the sequelae of venous disease: ulceration, chronic swelling and skin changes (liposclerosis, eczema, pigmentation). We used air-plethysmography because this non-invasive technique provides a reproducible measurement of venous reflux[8].

Material and methods

Air-plethysmography

The air-plethysmograph consisted of a 14 in. (≈35·6 cm) long tubular PVC air-chamber (5 litres capacity) that surrounded the whole leg. This was inflated with air to 6 mmHg and connected to a pressure transducer, amplifier and recorder. A PVC bag (1 litre capacity) was placed between the air-chamber and the leg and used for calibration.

Measurements were made at a room temperature of 22–24°C. The air-plethysmograph was fitted, with the patient in the supine position and the leg elevated (45°) to empty the veins, with the heel resting on a support. The air-chamber was inflated to 6 mmHg and the leg was kept in this position for at least 5 min to allow a stable leg/air-chamber/room temperature gradient and ensure a resting arterial inflow. A baseline was obtained and calibration was performed by injecting 200 ml water into the 1 litre bag, in increments of 50 ml at 37°C and observing the corresponding pressure changes in the air-chamber (*Figure 1*). The water was then removed.

The subject was asked to stand with the weight on the opposite limb, holding on to a frame. The foot of the limb being examined rested on the ground. An increase in the leg volume was observed in the recordings due to venous filling. The subject was asked to keep still until a plateau was reached indicating that the veins were full (*Figure 2*). This increase represented the functional venous volume (VV). The time taken to achieve 90 per cent of filling has been defined as venous filling time 90 (VFT90). The venous filling index (VFI) is obtained from VFI = 90 per cent VV/VFT90. This is a measure of the average filling rate of the veins and is expressed in ml s^{-1}.

The reproducibility of VFI has been determined in a previous study[8] where the coefficient of variation was found to be 5·3–7·9 per cent.

Leg volume measurements

The volume of the leg included in the air-plethysmograph was determined by water displacement. The leg was immersed in water initially to the ankle and subsequently to just below the knee according to skin marks made when the air-chamber was on the limb. The tissue

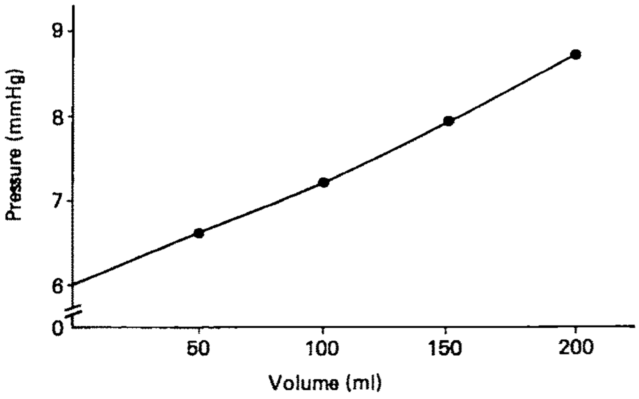

Figure 1 *Calibration curve obtained by injecting water at 37°C in increments of 50 ml into the bag used for calibration and observing the corresponding pressure in the air-chamber of the plethysmograph*

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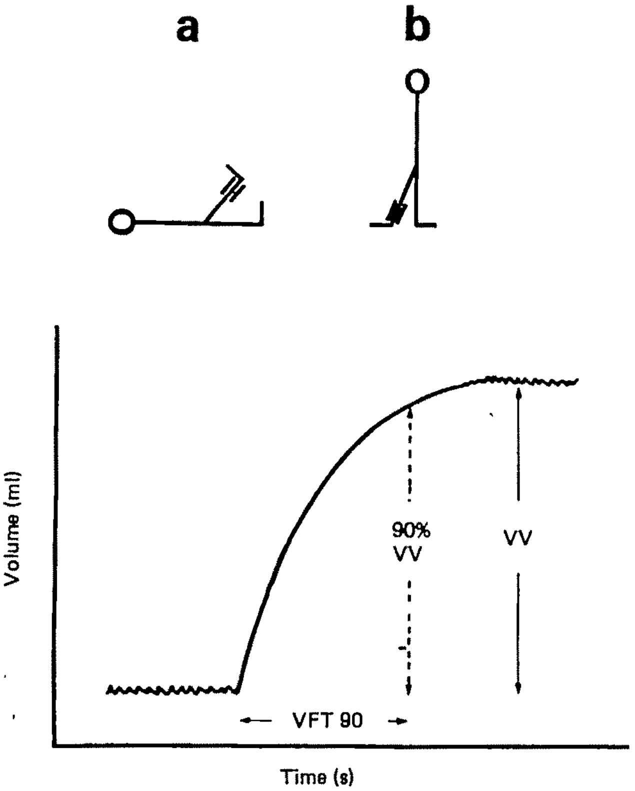

Figure 2 *Pressure changes of the air-chamber, recorded when the examined subject stood up from the horizontal position. The vertical axis represents the volume changes of the leg measured in ml according to the calibration. VV, functional venous volume (ml); 90 per cent VV, 90 per cent of the functional venous volume (ml), VFT90, venous filling time 90 (s)*

volume measurement was made so that the results of VFI, expressed in ml s^{-1}, could also be expressed as blood volume per unit volume of tissue per unit time; i.e. in ml 100 ml s^{-1} and ml 100 ml^{-1} min^{-1}. This enabled us to compare our measurements with similar measurements of other investigators.

Duplex scanning[9]

The Duplex scan (Advanced Technology Laboratories, Model 500) enabled the operator to visualize a particular vein by B-mode real-time ultrasound using a 7·5 mHz imaging probe, and to position a sample volume (2 × 3 mm) in its lumen by a gated directional 5 mHz Doppler beam. The popliteal vein behind the knee and the common femoral vein in the groin were examined

The popliteal vein was examined with the patient standing, facing away from the examiner and holding on to a railing or table. The knee on the side to be examined was flexed slightly (heel on the ground with foot slightly forward) so as to relax the popliteal fossa. The weight of the body was kept on the opposite limb This position ensured that the muscles of the leg were not contracting.

The probe was placed behind the knee pressing lightly on the skin and its position was adjusted so that three structures were identified on a longitudinal ultrasonic section of the popliteal fossa: the popliteal artery lying deepest, the popliteal vein more superficial and parallel to it and the short saphenous vein (SSV) most superficial. The latter had a smaller diameter and took an oblique course, joining the popliteal vein at the saphenopopliteal junction. The Doppler sample volume (2 × 3 mm) was positioned in the popliteal vein below the saphenopopliteal junction, when the latter was identified, and low in the popliteal fossa when it was not. A 60° angle between the Doppler beam and the vessel axis was used. The calf muscles were compressed by an assistant (although the procedure could also be carried out by a single examiner), demonstrating cephalad blood flow in the vein. After sudden release of calf compression, reverse blood flow indicated venous reflux. This could be both heard and seen as a negative deflection on the screen. Absence of such reflux indicated competent venous valves.

Whenever popliteal vein reflux was found, a below-knee tourniquet was applied to occlude the superficial veins and the test was repeated. This was to confirm that the reflux was in the popliteal vein itself and not into a low insertion of a non-visualized saphenopopliteal junction or any other incompetent deep-to-superficial communication.

The procedure was repeated in a similar way in the groin for detecting reflux in the common femoral vein. The patient was standing, holding on to a frame and facing the examiner with the weight mainly on the opposite limb. Provided that no previous surgery has been performed, the saphenofemoral junction is always demonstrated because of its constant anatomical position Longitudinal ultrasonic section of this area demonstrated the common femoral vein and the long saphenous vein with their junction. The sample volume was positioned 1–3 cm distal to the saphenofemoral junction. The calf muscles were compressed, demonstrating cephalad blood flow in the vein. Reverse blood flow after sudden release of calf compression indicated venous reflux. Whenever reflux was noted, a high thigh tourniquet was applied and the test was repeated to exclude any reflux into superficial veins.

Ambulatory venous pressure measurements[10]

A 21-gauge 'butterfly' needle was inserted into a vein on the dorsum of the foot and was connected through a pressure transducer to an amplifier and pen recorder The resting pressure was recorded with the patient in the standing position, holding on to a frame. The patient then performed a standard exercise of 10 tiptoe movements at the rate of 1 s^{-1}. At the end of exercise the patient remained still The ambulatory venous pressure (AVP) at the end of exercise was measured. This measurement was then repeated after inflating a pneumatic tourniquet 2·5 cm wide at the ankle to occlude the superficial veins[10].

The patients with an AVP <45 mmHg when the ankle tourniquet was inflated were considered to have primary varicose veins. Patients with an AVP >45 mmHg when the ankle tourniquet was inflated were considered to have incompetent deep veins.

Functional ascending venography

Ascending venography was performed using non-ionic low osmolar contrast medium (Hexabrix). The valves of the deep veins were shown using the technique described by Lundstrom and Osterman[11]. In addition to that technique, the reflux in the deep veins, especially the popliteal vein, was diagnosed as follows.

The patient was lying with the weight on the opposite leg with the X-ray table tilted 30° to the horizontal. A narrow (2·5 cm wide) pneumatic tourniquet at the ankle occluded the superficial veins. Contrast was injected into a foot vein and was followed with the image intensifier and seen to enter the deep veins of the calf As soon as the contrast reached the lower popliteal vein the calf was compressed manually. The contrast material was seen to fill the popliteal and femoral veins. The calf compression was then released Reflux of contrast into the calf veins indicated incompetent popliteal valves Lack of such reflux indicated functioning popliteal valves Reflux in the SSV was also visualized by performing the above procedure with the leg externally rotated to obtain lateral views

Calf compression and sudden release with Valsalva's manoeuvre was performed when contrast had reached the ileofemoral segment in order to visualize reflux in the femoral or long saphenous veins.

Subjects

Twenty-four normal volunteers (N) (24 limbs), 18 patients (21 limbs) with primary varicose veins but without sequelae of venous disease (ulceration, chronic swelling and skin changes such as liposclerosis, eczema or pigmentation) (PVV), 24 patients (31 limbs) with primary varicose veins, with sequelae of venous disease (PVV/S) and 25 patients (28 limbs) with popliteal reflux (PR) (*Table 1*) were studied In addition to clinical examination, all patients had been studied with Duplex scanning[9], AVP measurements[10] and ascending venography[11], as described above, so that the limbs could be classified as having superficial incompetence only with competent popliteal valves or deep

Table 1 *Subjects studied*

	N	PVV	PVV/S	PR
Number of subjects	24	18	24	25
Number of limbs	24	21	31	28
Age range (years)	25–64	25–56	22–85	24–61
Mean age (years)	38	41	51	49

N, normal limbs; PVV, limbs with primary varicose veins and no sequelae; PVV/S, limbs with primary varicose veins and sequelae; PR, limbs with popliteal reflux venous disease because of reflux in the femoral and popliteal vein. The normal volunteers were assessed clinically and with Duplex scanning to exclude asymptomatic superficial or deep venous reflux.

Saphenofemoral incompetence was detected in all the limbs with PVV or PVV/S except in two who had mid-thigh perforator incompetence (one with and one without sequelae of venous disease). Four of the limbs with saphenofemoral incompetence (two with PVV and two with PVV/S) had saphenopopliteal incompetence also and twenty-seven (eight limbs with PVV and nineteen with PVV/S) had incompetence of the calf-perforating veins. In the group of patients with PR, eight limbs had reflux in the femoral vein too. Chronic venous obstruction was excluded by venography in all the patients because the aim of this study was to evaluate the effect of reflux without interference from other causes of venous hypertension. Air-plethysmography and leg volume measurements were made in all limbs as described above.

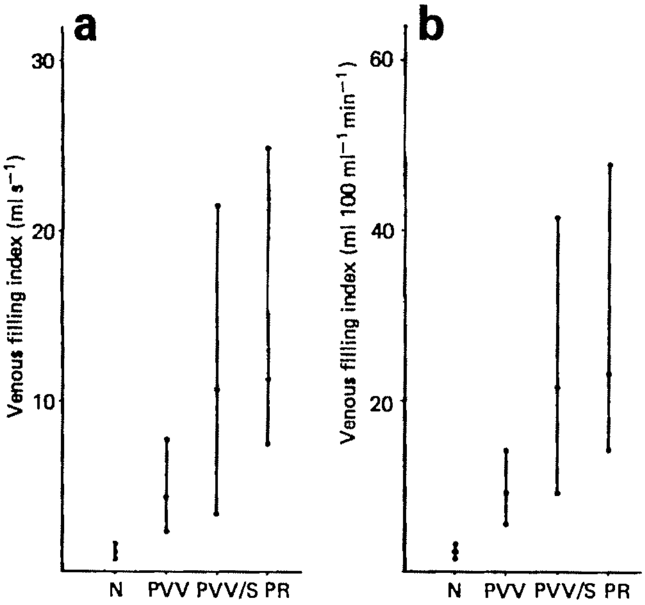

Figure 3 *The measurements of venous filling index in the four groups of limbs examined* (**a**) *in ml s^{-1} and* (**b**) *in ml 100 ml^{-1} min^{-1}. The results are shown as median and 90 per cent tolerance levels (90 per cent range) N, normal limbs; PVV, limbs with primary varicose veins without sequelae; PVV/S, limbs with primary varicose veins with sequelae, PR, limbs with reflux in the popliteal vein*

Sixteen of the patients with primary varicose veins (22 limbs) underwent venous surgery subsequently. Five limbs had chronic ulcers (three healed and two active), two limbs had chronic swelling with excessive pigmentation and liposclerosis, and three limbs had recurrent varicose veins, the first operation being performed 3–7 years ago. Incompetence of the saphenofemoral junction was detected in all the limbs with PVV except one who had mid-thigh perforator incompetence. Two of the limbs with saphenofemoral incompetence had saphenopopliteal incompetence too and seven had incompetence of the calf-perforating veins.

Stripping of the long saphenous vein was performed in 7 limbs, ligation of the saphenofemoral junction in 14 limbs and ligation of the mid-thigh perforator in 1 limb. In addition, short saphenous ligation was performed in 2 limbs, avulsions in 15 limbs and ligation of incompetent calf perforators, with small skin incisions, in 7 limbs. The limbs were bandaged at the end of the operation. Seven days after operation the patient's limbs were assessed clinically and with Duplex scanning No residual reflux could be detected.

These limbs were studied with air-plethysmography, as described, the day before operation and on the eighth postoperative day.

Results

The measurements of VFI are shown in *Figure 3a* in ml s^{-1} and in *Figure 3b* in ml 100 ml^{-1} min^{-1}. They are expressed as median and 90 per cent tolerance levels (90 per cent of range). The VFI in normal limbs was less than 1·7 ml s^{-1}. In limbs with PVV, VFI was between 2 and 9·5 ml s^{-1}; in limbs with PVV/S it was between 3 and 30 ml s^{-1} and in limbs with PR between 7 and 28 ml s^{-1}.

The distribution of chronic swelling, ulceration and skin changes in the three groups of patients (PVV, PVV/S and PR) are shown in *Figures 4a, 4b* and *4c* respectively. The incidence of these sequelae of venous disease is low for a VFI less than 5 ml s^{-1}. It increases with an increase in VFI (*Table 2*).

The values of the VFI before and after surgery are shown in *Figure 5*. In 12 limbs the operation normalized VFI (<2 ml s^{-1}). The VFI was markedly decreased in the remaining 10 limbs, from the range of 5–30 ml s^{-1} to the range of 2–5 ml s^{-1}. This last group consisted of limbs with ulcers, chronic swelling with excessive liposclerosis and pigmentation, and recurrent varicose veins.

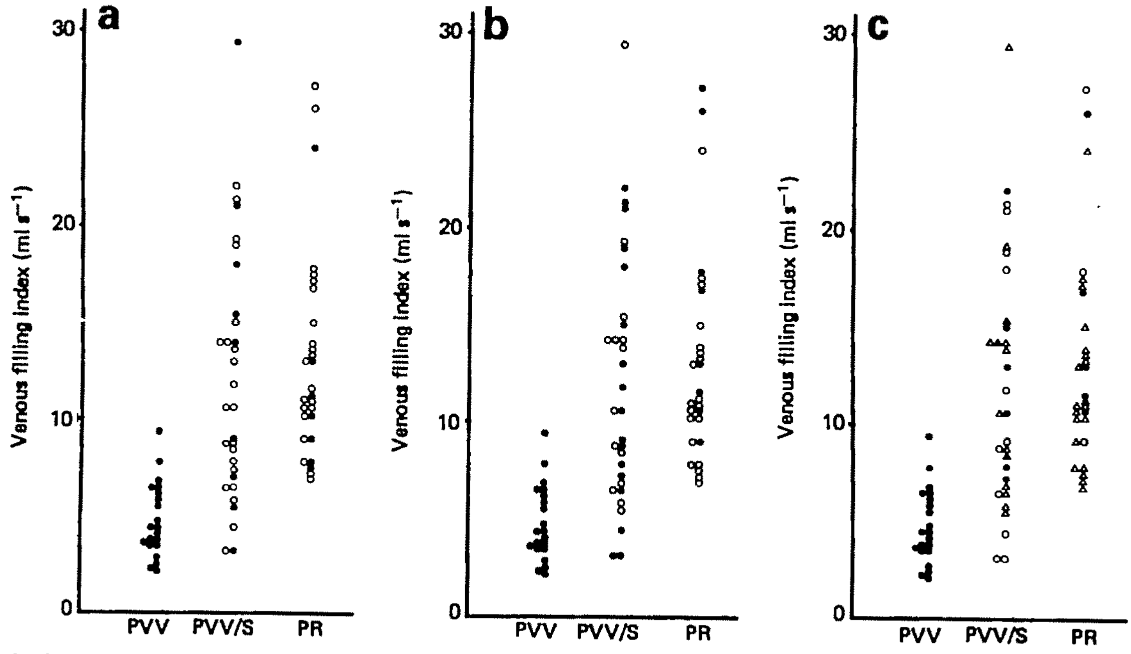

Figure 4 *The distribution of chronic swelling* (**a**), *ulceration* (**b**), *skin changes (liposclerosis, eczema, pigmentation) with or without ulceration* (**c**), *in relation to the venous filling index measurements. PVV, Limbs with primary varicose veins without sequelae, PVV/S, limbs with primary varicose veins with sequelae; PR, limbs with reflux in the popliteal vein.* **a**: ●, *no chronic swelling;* ○, *chronic swelling;* **b**: ●, *no ulceration;* ○, *ulceration,* **c**: ●, *no skin changes or ulceration;* ○, *skin changes;* △, *ulceration*

Table 2 *Incidence of the sequelae of venous disease in relation to venous filling index in the 80 limbs with venous disease studied*

VFI ($\mathrm{ml\,s^{-1}}$)	Chronic swelling (%)	Ulceration (%)	Skin changes with or without ulcer (%)
<3	0	0	0
3–5	12	0	19
5–10	46	46	61
>10	76	58	76

VFI, venous filling index

Discussion

The Brodie and Trendelenburg test is the traditional clinical method for the diagnosis and localization of venous reflux. This test is tedious to perform and often difficult to interpret when the varicosities are not prominent[12]. The use of Duplex scanning in the examination of the patient with venous problems[9] provides an accurate detection and localization of venous reflux in the superficial or in the deep system. Unfortunately, quantification of reflux in the leg as a whole cannot be obtained with these methods although Duplex scanning has the potential to measure reflux in individual veins.

Several previous attempts have been made to quantify venous reflux. Segmental plethysmographic devices[13–16] and isotopes[17] have been used to measure the venous filling rate of the calf, either after high compression using a rapidly inflated tourniquet[15] or by gravity[13–16]. Our data are in agreement with the observations of Sakaguchi and associates[14] in limbs with primary varicose veins and with the findings of Barnes and associates[15] in normal limbs and in limbs with deep venous disease. Several problems have been reported[13] when quantifying reflux with segmental plethysmographs because tissue shifts which occur while changing posture interfere with the measurements[18]. Such interferences did not occur in the present study, probably because the air-chamber of the air-plethysmograph included the whole leg from knee to ankle.

Venous reflux under physiological conditions is the result of gravity. For this reason we emptied the veins using leg elevation and measured the filling rate by asking the patient to stand up. By avoiding any form of exercise or calf compression to empty the veins[14], or artificially forcing blood distally by inflating a thigh tourniquet[15] we avoided unphysiological situations, hyperaemia and interference from other uncontrolled variables such as the amount of blood ejected proximally or distally by compression or exercise.

Relaxation of the examined leg was achieved by asking the patient to place his weight on the opposite leg and to keep holding on to a frame for stability. The use of the frame avoided any calf muscle contractions and ensured a good reproducibility (coefficient of variation of VFI 5·3–7·9 per cent)[8].

We have defined the VFI as the ratio of 90 per cent of the functional VV over the equivalent time required for the filling of the veins on standing from the supine position (VFT90). We have taken this measurement because the VFT90 can be determined more precisely than the total filling time, from the recordings.

Data from the control group of normal volunteers (N) indicate that the VFI in normal limbs is 0·6–1·7 $\mathrm{ml\,s^{-1}}$ (*Figure 3*). This reflects the rate of venous filling from normal capillaries, at rest. A VFI $>2\ \mathrm{ml\,s^{-1}}$ indicates the presence of venous reflux, provided it is measured after 5–10 min of rest and in the absence of arteriovenous fistulae.

As shown in *Figure 4* and *Table 2*, the incidence of ulceration, chronic swelling and skin changes increases with increased VFI, making VFI not only a measurement of venous reflux, but also a useful index of the severity of venous disease. In addition, it has been demonstrated that the increase in the incidence of sequelae in relation to increasing rates of reflux occurs irrespective of whether the reflux is in the superficial or the deep veins.

Figure 4b also shows that 16 patients with a VFI $>10\ \mathrm{ml\,s^{-1}}$ did not have ulcers (dark dots), indicating the possibility of a number of protective factors. Perhaps in some of these patients the condition has not been present long enough or they have a very efficient fibrinolytic mechanism and lymphatic system that can remove the extravascular fluid and pericapillary deposition of fibrin responsible for the chronic sequelae[19]. Another possibility is the presence of a calf muscle pump with such a high ejection fraction that it can reduce ambulatory venous pressure to safe levels despite the high amount of reflux. Further work is needed with measurement of fibrinolytic activity, lymphatic drainage and ejection fraction to test the above hypotheses.

The abolition of venous reflux by surgery has also been demonstrated. As shown in *Figure 5*, after operation the limbs with uncomplicated varicose veins had a reduced but not normalized VFI in all limbs. This persisting high VFI is very unlikely to be due to residual reflux, because the pre-operative assessment had been extensive, surgery had been meticulous and after operation no residual reflux had been detected with Duplex scanning. A possible explanation is the existence of dilated capillaries in the lower limb, which act as 'arteriovenous fistulae[19–23], in patients with long-standing venous disease. Further research is required to investigate this also.

The measurement of VFI apart from its diagnostic value provides an objective way to evaluate the results of venous surgery. The control of reflux in the superficial veins by established surgical techniques has been demonstrated by using this non-invasive quantitative method of air-plethysmography. The success of new operations designed to abolish reflux in the deep veins[2–6] should also be studied with the same technique.

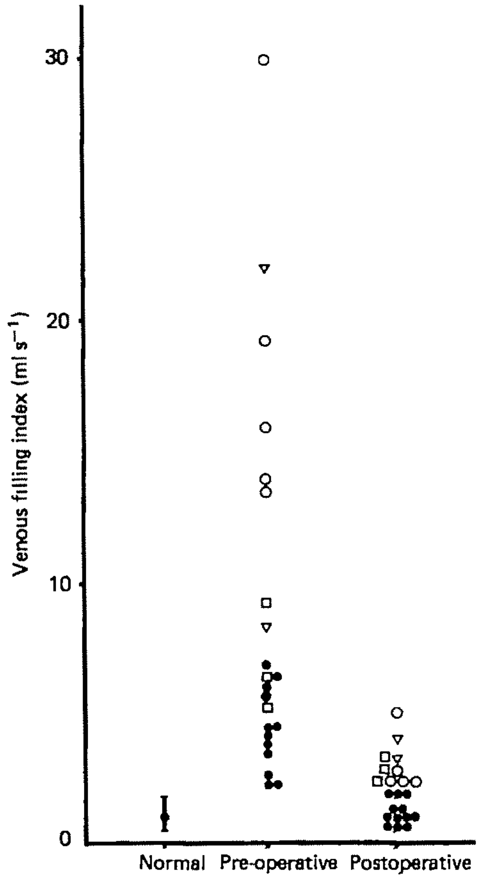

Figure 5 *The measurements of the venous filling index (VFI) before and after operation in limbs with primary varicose veins and normal deep system. N, normal range; ○, venous ulcer; ▽, chronic swelling and skin changes, □, recurrent varicose veins, ●, uncomplicated varicose veins*

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Evaluation of peritoneal tube grafts in the inferior vena cava of the pig

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A tube graft 2·5 or 5 cm long, was constructed from the peritoneum of the anterior abdominal wall of 12 pigs. It was anastomosed end-to-end as an interposition graft in the infrarenal vena cava. The observation period was 4 months. Three of the six short grafts were venographically patent at 2 weeks, while all the long grafts were occluded. After 4 months two short grafts had recanalized, giving a patency rate of five out of six short grafts. No long grafts recanalized. In three of the patent specimens no clear tissue changes were found with light microscopy, while in the others changes of inflammation and fibrosis were noted. Scanning electron microscopy revealed good 'endothelialization' in two specimens, and partial 'endothelialization' in the others. No dilatation or severe stenosis of the patent grafts was seen. The occluded grafts remained only as a fibrous strand with sutures.

Keywords: Peritoneum, graft, inferior vena cava

Reconstructions of veins meet with greater difficulties than do arterial reconstructions. This has been attributed to the low flow rate and the low pressure in veins and to 'antigravitational' flow in veins of the lower part of the body. There is a need for reconstructions of major veins in, for example, cases of advanced tumour surgery and of major venous trauma.

So far no ideal graft material for veins has been found. The peritoneum is readily available in large quantities for construction of an autologous graft. In earlier experiments in rats we studied peritoneal tube grafts in the inferior vena cava and found a patency of eight out of ten grafts at 4 months[1,2]. Studies of platelet aggregation immediately postoperatively on peritoneal tube grafts in pigs have revealed only limited aggregation[3], supporting the possibility of using this tissue as a vascular graft.

The aim of this study was to evaluate peritoneum as a material for interpositional tube grafts for the inferior vena cava in pigs during an observation period of 4 months.

Materials and methods

Twelve Swedish domestic pigs weighing about 20 kg were used. Anaesthesia was induced with intravenous thiopental sodium (Pentothal, Abbot, Sweden) followed by infusion of ketaminum (Ketalar, Parke-Davis, USA) or with azaperonum (Stresnil vet., LEO, Sweden) and metomidatum (Hypnodil, Janssen Pharmaceuticals, Belgium). A total of 200 000 units of benzylpenicillin and 200 mg dihydrostreptomycinsulfate (Penicillin-dihydrostreptomycin vet., Hoechst, FRG) were given intramuscularly.

Surgical procedures

Surgery was performed under sterile conditions and the anastomoses were performed using optical magnification (×2·5).

Through a midline incision the infrarenal vena cava was exposed. A piece of peritoneum from the anterior abdominal wall below the xiphoid process was cleaned from fat and excised. It was then cut into a rectangle, after which a tube was sewn using a 2 ml syringe (diameter 11 mm) as a stent. The longitudinal suture was performed with everting technique using interrupted 6-0 polypropylene (Prolene, Ethicon, UK) sutures. The graft was kept moist with heparinized saline. In group A (6 pigs) 1–2 cm of the vena cava was excised and in group B (6 pigs) 3–4 cm was excised.

The peritoneal tube graft was anastomosed as an interposition graft to the vena cava with end-to-end anastomoses. In group A the graft was 2·5 cm long and in group B it was 5 cm long. The posterior part of the anastomosis was performed with continuous everting 6-0 Prolene sutures and the anterior part with interrupted everting 6-0 Prolene sutures.

No systemic heparinization was used, but the ends of the vein were rinsed with heparinized saline and the graft was filled with this solution before the last suture. Patency was verified after about 20 min, after which the abdominal wound was closed.

The duration of the operation was 2–2·5 h and clamping time was about 35 min.

Two weeks after surgery all the animals were re-anaesthetized as previously described and, via a right groin incision, a catheter was introduced into the right femoral vein and the tip was placed in the iliac vein. Phlebography with two films was then performed in the anterior-posterior position using 20 ml of contrast medium (Isopaque Cerebral, meglumine diatrizoate, 280 mg iodine/ml, Nyegaard and Company, Norway) to establish patency or occlusion.

During the observation period (median 115 days, mean 113 days, range 100–124 days) the animals lived the lives of ordinary Swedish domestic pigs on a farm.

The pigs were re-anaesthetized at the end of the study, and phlebography repeated in four of the six animals in group A and in all six animals in group B. In two animals it was not possible to obtain radiological pictures, for technical reasons. The graft area was next freed from the retroperitoneum and fibrosis and possible collaterals were observed. Patency was evaluated by inspection after which the graft area was excised.

Microscopical examination

Longitudinal slices from the patent grafts with adjacent anastomoses and vena cava as well as slices from native peritoneum were fixed in 10 per cent formol and further processed for paraffin embedding. Sections, cut at a thickness of 8 μm, were stained with haematoxylin and eosin and van Gieson's method for connective tissue.

Scanning electron microscopical evaluation

Slices from the patent grafts with adjacent anastomoses as well as vena cava and slices of normal peritoneum were placed in a glutaraldehyde solution (composition: 0·2 M phosphate buffer 400 ml, 50 per cent glutaraldehyde 50 ml, 20 per cent dextran T70 95 ml, distilled water 455 ml). After about 24 h the specimens were rinsed in Millonig's phosphate buffer five times. They were then dehydrated in increasing concentrations of alcohol and immersed in increasing concentrations of Freon TF (Dupont, The Netherlands), after which they were dried at the critical point. They were finally mounted on holders and sputter-coated with gold-palladium. They were then examined and photographed, using a scanning electron microscope (Nanolab 2000 Zeiss).

Results

All the animals survived the operation and the subsequent observation period and gained weight normally. At the end of the study the weight of the animals was about 80 kg.

Phlebography

At phlebography 2 weeks after surgery three grafts in group A

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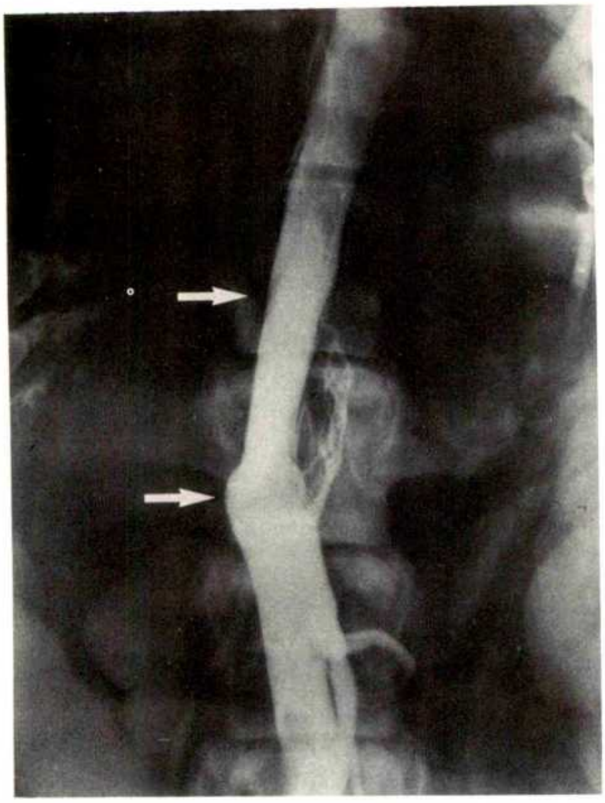

Figure 1 *Patent peritoneal graft after 4 months. There are no signs of stenosis in the anastomoses. Note the filling of one collateral. This graft was found to have a stenosis in the cranial anastomosis 2 weeks postoperatively. Arrows point at the anastomoses*

were patent, whereas all the grafts in group B were occluded. In one of the patent grafts there was a stenosis at the cranial anastomosis, and there was filling of one collateral. In the animals with occluded grafts an abundant filling through collaterals from below the anastomoses was seen.

Phlebography after 4 months revealed that three of the four examined grafts in group A were patent. The graft with a stenosis at 2 weeks was patent and there was no longer any stenosis (*Figure 1*). The collateral, however, remained. One graft, occluded at 2 weeks, had recanalized but showed an irregular picture (*Figure 2*). One graft in group A and all the grafts in group B were occluded and around these there was a large amount of collaterals.

Macroscopical evaluation

None of the animals showed any signs of infection at relaparotomy. Macroscopically five of the six grafts in group A were patent at the end of the study, while all grafts in group B were occluded. Two of the grafts in group A that were occluded at 2 weeks had recanalized. However, their lumina were partially somewhat irregular and showed small veils as signs of the recanalization. The patent grafts had no stenoses in the anstomoses. Furthermore, no aneurysmal dilatations of the grafts or anastomoses were seen. Few collaterals existed. The surrounding tissue was fairly fibrous, especially along the longitudinal suture of the graft.

The occluded grafts were totally obliterated and could be identified mainly as a fibrous strand with remaining sutures.

Light microscopy

The native peritoneum was a membraneous structure consisting of densely packed collagen and elastic fibres with scattered fibroblasts and with few blood vessels passing through the wall. The surface was covered with thin flattened cells with elongated nuclei. Three of the patent peritoneal tube grafts were well healed into the adjacent vena cava with no clear tissue changes and no signs of necrosis or inflammation. There was slight to moderate fibrosis in the anastomotic regions. Two of these grafts were found occluded two weeks postoperatively, but were patent at the end of the study. One graft showed slight to moderate oedema and diffuse bleeding in the wall with some splitting and degeneration of the tissue. In one graft there was diffuse inflammatory reaction and fibrosis and along the longitudinal suture focal calcification and even bone formation was found.

Scanning electron microscopy

It was not possible to obtain surface pictures from the occluded grafts. In the others there was a varying degree of cell covering. Two grafts were totally covered with elongated cells with prominent, rounded nuclei of endothelial-like appearance. Few microvilli were seen (*Figure 3*). These grafts were found to be patent both at 2 weeks postoperatively and at the end of the study and microscopical appearance of the wall revealed no or only slight changes. Remaining grafts were only partially covered with endothelial-like cells. The rest of the surface was covered with a rough, wave-like structure, devoid of cell structures (*Figure 4*). The specimens from native peritoneum showed a rough surface where mesothelial cells were damaged and irregular. An abundance of microvilli was seen. These specimens differed significantly from the covered graft surfaces.

Discussion

In the area of venous reconstruction no graft material has been found superior to autologous vein. However, there is a lack of suitable veins for large vein repair. To overcome this, doubling or cross-turning of the harvested vein[4] has been developed as has the spiral grafting procedure[5]. These require a time-consuming and meticulous technique. Results with polytetrafluoroethylene (PTFE, GORE-TEX, W. L. Gore and Associates Incorporated, UK) grafts in the inferior vena cava

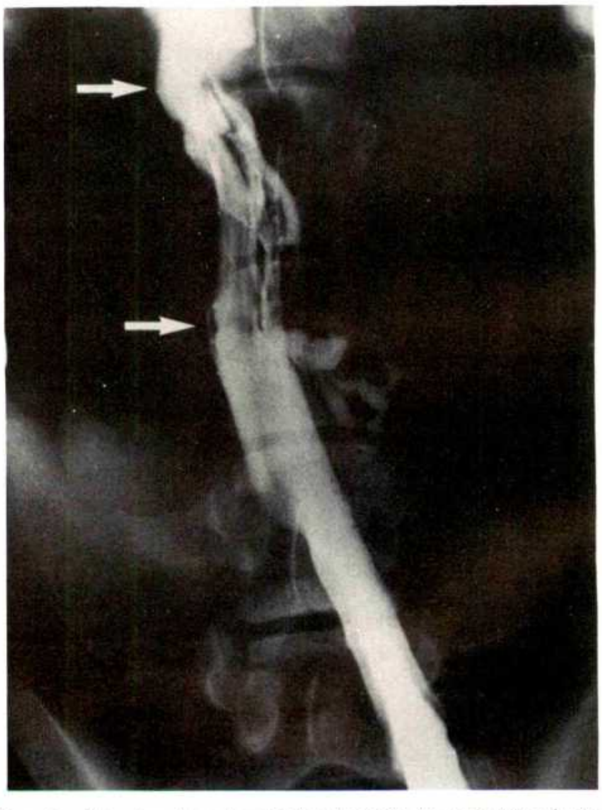

Figure 2 *Patent peritoneal graft after 4 months. Note the irregularity of the graft wall. Filling of one collateral is seen. This graft had recanalized between 2 weeks and 4 months postoperatively. Arrows point at the anastomoses*

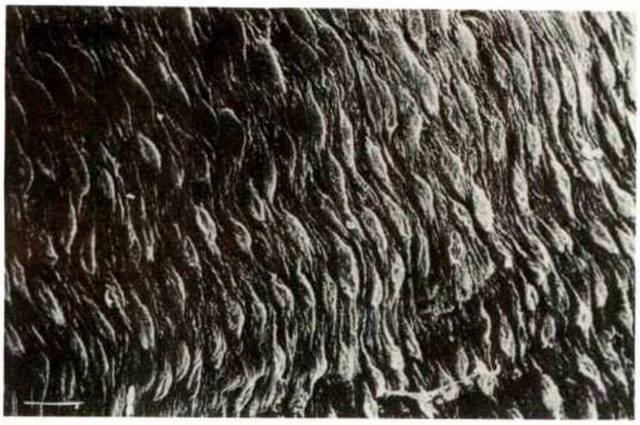

Figure 3 *Scanning electron micrograph of a patent peritoneal graft. The whole surface is covered with elongated cells with prominent, rounded, nuclei with the long axis oriented in the direction of flow. (Original magnification ×600, scale bar 15 μm)*

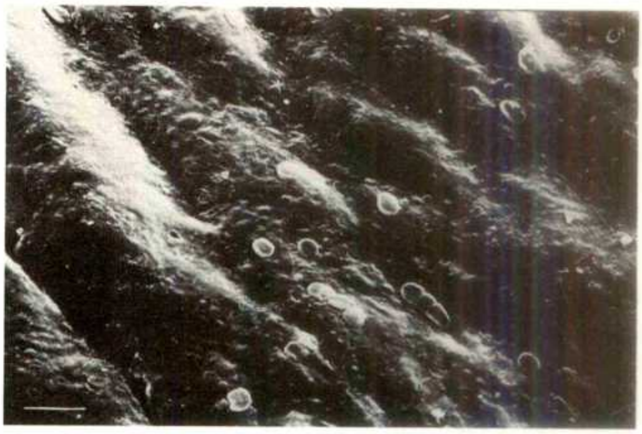

Figure 4 *Scanning electron micrograph of a patent peritoneal graft. On the surface no endothelial cells are seen, but the surface is covered with a rough, wave-like structure, devoid of obvious cells. (Original magnification ×600, scale bar 15 μm)*

have been promising[6]. An easily available autologous material suitable as a graft would, however, be desirable. Autologous peritoneum is an interesting material to try for venous grafting. Its mesothelium originates embryologically from the same stem cell as the endothelium, giving the two surfaces several properties in common, e.g. prostacyclin production[7] and fibrinolytic activity[8].

Peritoneal tube grafting has previously been reported and a common feature has been early occlusions unless some adjuvant treatment was used. Thus Baumann[9] and Louagie *et al.*[10] achieved improved patency rates with an arteriovenous fistula, whereas Price-Thomas *et al.*[11] used antithrombotic drugs (phenylbutazone). External support of the graft was used with improvement by Baumann[9] and it is also applied clinically with PTFE grafts[12,13]. A tendency for graft and anastomotic strictures has been found, a reaction that might be augmented by the inclusion of the posterior rectus sheath in the graft. To reduce this risk we did not include the rectus sheath in our grafts and stenosis or stricture was not found in our patent grafts at the end of the study.

Our results after 4 months showed five out of six patent short grafts, while none of the longer grafts remained patent. One probable reason for the occlusions is that the graft wall is thin and soft and may easily be squeezed by external pressure as the intravascular pressure is low. Another reason for the graft failures might be thrombotic occlusion. However, we studied platelet aggregation on peritoneal tube grafts in the vena cava directly postoperatively, using dynamic recording of radiolabelled platelets. Our results indicate a low tendency for platelet aggregation. Clarke *et al.*[14] found in an *in vitro* model that uninjured mesothelium did not aggregate platelets whereas damaged mesothelium did. In pilot experiments we found a partial desquamation of mesothelial cells after preparation and construction of the tube graft, mimicing the experimental situation in this study. It is also probable that the mesothelial cells do not retain their prostacyclin production or fibrinolytic activity in the immediate postoperative period[15]. Theoretically the remaining mesothelial cells merely serve as a good matrix for regeneration of cells or deposition of circulating endothelial cells.

Another possible reason for the occlusions of the long grafts in this study might be the longitudinal suture line which might induce fibrosis. The light microscopical changes found in our patent grafts indicated that the major reactions occurred along this suture line. Improvement of this technique, e.g. with the use of sealing agents or laser[16], might be beneficial.

The surface of the patent grafts in this study did not show any uniform 'endothelialization'. Only two grafts were fully covered with endothelial-like cells. The walls of these grafts showed no or slight microscopical changes. There was no indication that recanalization had occurred in these grafts. Remaining patent grafts were only partially covered with endothelial-like cells. Two of these grafts had recanalized, as judged by phlebography.

It is known that contrast medium used for phlebography might damage endothelial cells[17]. However, it is less likely that the difference in 'endothelialization' in this study was caused by the phlebography as one of the totally 'endothelialized' grafts had been subjected to phlebography whereas the other had not. The cells covering the grafts looked like endothelial cells and were continuous with the endothelial cells of the native vein. Few microvilli were seen. However, to ascertain whether the cells were of mesothelial or endothelial origin transmission electron microscopical studies had been necessary to detect the presence or absence of Weibel–Palade bodies, seen only in endothelial cells[18]. In human veins, recanalization usually occurs within the first year after thrombosis, whereas it is known to develop faster in animals[19]. In this study recanalization of two short grafts occurred within 4 months. As no valves are present in the vena cava recanalization there produces no detriment in venous function as it does in valve-containing peripheral veins.

In summary this study revealed a long-term patency rate of five out of six short peritoneal tube grafts, whereas all longer grafts occluded. An early recanalization of short grafts was found. It is concluded from this study that only short peritoneal tube grafts will retain patency in the vena cava without adjuvent measures such as anti-platelet drugs, external support or an arteriovenous fistula.

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Case report

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Erosion of rectum by Tenckhoff catheter

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Continuous ambulatory peritoneal dialysis via a Tenckhoff catheter is now a major part of the British renal replacement programme[1]. Blockage of the catheter, leakage of the dialysate from the peritoneal cavity, the development of hernias and catheter-related peritonitis are common complications[2,3]. Most episodes of catheter-related infection respond to intraperitoneal antibiotics but recurrent or persistent sepsis requires catheter removal, although immediate replacement at the same operation may sometimes be satisfactory[4]. Culture of bowel organisms in catheter-related sepsis, particularly of more than one species, should alert the clinician to the possibility of visceral involvement.

Case report

A 46-year old caretaker presented with chronic renal failure attributable to polycystic kidney disease in 1985. A Tenckhoff catheter was inserted into the pelvis under general anaesthetic. As a result of recurrent peritonitis from a coagulase-negative staphylococcus the catheter was removed and a second catheter inserted after a period of haemodialysis. Subsequently he developed an incisional hernia in which small bowel became entrapped. The hernia was explored and the bowel was released and found to be viable. The Tenckhoff catheter was removed and another inserted into the pelvis under direct vision at the time of the incisional hernia repair. After this operation he developed minor wound sepsis from which *Proteus* was cultured. The discharge persisted intermittently though the patient was never systemically unwell. Haemodialysis was continued because a wound sinus persisted. *Bacteroides fragilis* and *Escherichia coli* were later grown from a sinus in the wound. The patient was otherwise asymptomatic and it was only the persistence of the sinus for a further month that called for a sinogram which demonstrated a communication between the sinus, the catheter within the pelvis and the rectum. The catheter was simply removed at operation and the wound left open to granulate. Healing occurred without sepsis and the patient is now on permanent haemodialysis.

Discussion

Intraperitoneal drains do occasionally erode adjacent structures; their prolonged use is therefore discouraged. The presence of a Tenckhoff catheter in the pelvis is associated with relatively few serious complications, presumably because it is soft, inert and separated from the adjacent viscus by dialysate. Prolonged periods of non-use of a Tenckhoff catheter are quite common although complications seem unusual. In one case report, erosion of the caecum followed a period of non-use of the catheter at the time of renal transplantation; the patient did not show signs of sepsis and the diagnosis was made only on the passage of clear watery stool during infusion of the dialysate[5]. Similarly, in the case reported here, the catheter had eroded into the large bowel without signs of acute systemic sepsis. Both patients recovered without complications after removal of the catheter. The commonest organism isolated from catheter-related peritonitis without gut involvement is *Staphylococcus epidermidis* although *S. aureus* and *Pseudomonas* species are sometimes seen. The presence of *B. fragilis* and *E. coli* is unusual and should lead to suspicion of gut involvement.

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Pulse-generated runoff: a new method of determining calf vessel patency

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A non-invasive method of determining calf vessel patency before femorodistal bypass has been developed. This pulse-generated runoff (PGR) system generates blood flow in patent calf arteries by means of a pulsatile cuff even if the existing Doppler signal is inaudible. PGR was compared with pre-operative arteriography in 95 ischaemic limbs and both were compared with the peripheral resistance measured at operation in 62 limbs. There was a highly significant correlation between the PGR and arteriogram scores ($r_S = 0{\cdot}74$, $P < 0{\cdot}001$) *but PGR tended to detect more patent vessels than arteriography. The peripheral resistance correlated better with PGR than arteriography* ($r_S = -0{\cdot}71$ *and* $-0{\cdot}54$ *respectively,* $P < 0{\cdot}001$). *PGR is a simple, non-invasive method of determining calf and foot vessel patency pre-operatively.*

Keywords: Arteriosclerosis, femoropopliteal bypass, Doppler ultrasound, arteriography

The decision to attempt a femorodistal bypass graft is usually based on the pre-operative demonstration of an adequate calf vessel runoff. It is an advantage to know the state of the runoff vessels as this may affect the level of the distal anastomosis and influence graft patency[1]. When the popliteal artery is occluded it is essential to detect which calf vessel, if any, is patent as this will determine whether grafting is at all possible. Assessment of the pedal arch and its calf vessel connections may also influence the site of the distal anastomosis[2].

The recent upsurge in popularity of femorodistal grafts for limb salvage[3] has highlighted the shortcomings of conventional pre-operative arteriography. About one-quarter of crural or pedal arteries that are judged patent on Doppler ultrasonography or direct operative exploration may fail to opacify[4–6]. The use of specialized techniques such as reactive hyperaemia[7], vasodilators[8], intra-operative arteriography[6], or digital subtraction arteriography[9] may increase the visualization of distal vessels but they are not always practicable or available.

Doppler ultrasonography may detect patent crural or pedal vessels that are missed on arteriography but may itself miss patent vessels because of severely damped signals owing to a low perfusion pressure[5]. Diligent searching over the area of the vessel without pressure from the probe on the skin and increasing the perfusion pressure by making the feet dependent may help, but these require patience and expertise.

A novel system to enhance the detection of patent calf vessels by Doppler ultrasound has been developed. The pressure-generated runoff (PGR) system was compared with pre-operative arteriography and both methods were compared with the peripheral resistance measured at operation which is a more physiological measure of runoff[10].

Patients and methods

Instrumentation

The simple non-invasive system is based on a standard 10 MHz Doppler ultrasound velocimeter and a sphygmomanometer cuff driven by pulsatile compressed air. The cuff is placed around the upper calf and the pulsatile pressure generates blood flow in the calf arteries (*Figure 1*). Patent arteries can be detected by the Doppler probe at the ankle even if the existing signal is inaudible. The pedal arch patency test[11] is also easily performed to determine continuity with the pedal arch. An occlusive thigh cuff is occasionally required to prevent interference by the normal arterial signal although it is not usually necessary in severely ischaemic limbs. Venous signals are readily differentiated from arterial ones as they are characteristically attenuated by the venous valves which prevent retrograde flow. Theoretically there might be a problem in patients with deep venous incompetence but this has not been encountered clinically.

The control unit is driven by compressed air and consists of two separate modules controlling the pulsatile and occlusive cuffs. The inflation and deflation of the pulsatile cuff is controlled by a two-way solenoid valve and an in-line solid-state pressure transducer. The pulse pressure can be varied from 0 to 300 mmHg and the frequency of pulsation from 0 to 100/min but a standard pulse of 250 mmHg at a rate of 50/min is usually used. The occlusive cuff pressure is controlled by a standard pressure regulator and can be varied from 0 to 300 mmHg.

Scoring

Using the PGR system a search was made for all three calf vessels at the level of the ankle (anterior tibial, posterior tibial and peroneal arteries). Each vessel was scored 2 for a normal biphasic signal, 1 for a damped monophasic signal and 0 for no signal, giving a possible total of 0–6. A normal signal has a sharp upstroke as the cuff inflates, an amplitude >2 cm and reversed flow as the cuff deflates (*Figure 2*).

The pre-operative arteriograms were scored at a weekly meeting of the consultant vascular surgeons and radiologists. Each calf vessel was scored 2 if patent to the ankle, 1 if patent but diseased and 0 if occluded, again giving a possible total of 0–6. Arteriograms were judged to be inadequate if there was no filling of calf collaterals on any of the series. Assessment of the plantar arch proved to be impossible because it was rarely adequately demonstrated.

Patients

Ninety-five ischaemic limbs with superficial femoral artery occlusion were studied in 76 patients (49 men and 27 women, aged 42–92 years, median 76 years). Of these limbs, 68 were critically ischaemic with rest pain and/or gangrene and 27 had symptoms of claudication only. All

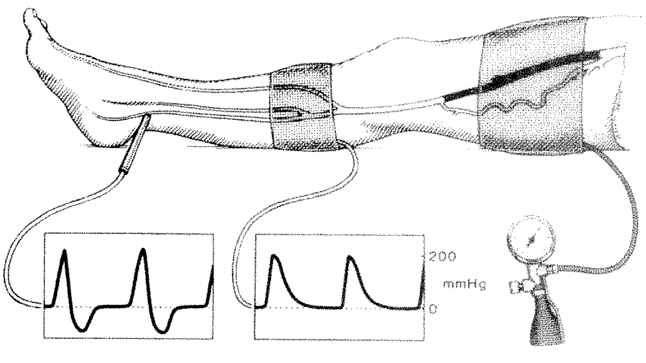

Figure 1 *Outline of the pulse-generated runoff system*

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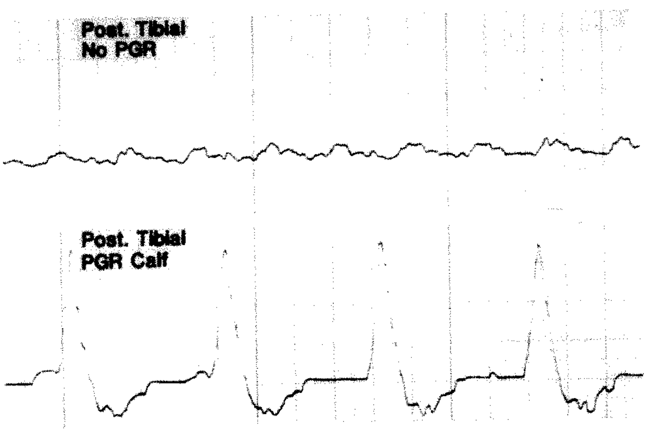

Figure 2 *Pulsatile flow produced by the PGR system in a patent posterior tibial artery. The existing flow was virtually inaudible and the vessel failed to opacify on pre-operative arteriography*

patients underwent transfemoral aortography except for six who had unilateral femoral arteriograms. PGR assessments were made on all limbs within 24 h of arteriography.

Ten control limbs were studied in five patients with isolated aorto-iliac disease, whose arteriograms demonstrated three patent calf vessels down to the ankle.

Peripheral resistance

The peripheral resistance was measured in all of the 62 limbs undergoing femorodistal reconstruction or amputation. Of the 62 limbs, 9 received a primary amputation based upon the pre-operative arteriogram and the degree of tissue loss. The remaining 53 underwent exploration with a view to reconstruction, and of these: 5 received a below-knee amputation, the other 48 received an *in situ* femorodistal vein graft. The decision to amputate was made by the consultant surgeon if the distal vessels were occluded or severely diseased. The distal anastomosis was to the infrageniculate popliteal in 29 limbs, the tibioperoneal trunk in 10 and to a calf vessel in 9 limbs.

The peripheral resistance was measured by a method similar to that described by Parvin^{10}. An infusion of heparinized blood was made by hand, via a soft 6 or 8 French PVC catheter inserted through an arteriotomy into the vessel chosen for the distal anastomosis. The resistance was calculated from the simultaneously recorded pressure and flow, a deduction being made for the resistance of the catheter. The resistance in the primary amputation group was measured in the calf vessel thought best on exploration before amputation.

Results

The 10 control limbs with arteriogram scores of 6 all scored 6 on the PGR assessment. Seventeen arteriograms (18 per cent) were judged inadequate for scoring leaving seventy-eight for comparison with the PGR (*Figure 3*). There was a highly significant correlation between the arteriogram and the PGR scores (Spearman's rank correlation, 0·74; $P<0{\cdot}001$). In severely ischaemic limbs the PGR tended to detect more vessels than arteriography, detecting at least one patent vessel in eight limbs (8 per cent) where no vessel was judged patent and in sixteen limbs (17 per cent) where the arteriogram was judged inadequate.

The peripheral resistance, measured in the 62 operated limbs, correlated better with the PGR than the arteriogram score (*Figure 4*) although both were highly significant (Spearman's Rank Correlation, −0·71 and −0·54 respectively; $P<0{\cdot}001$). There was a highly significant difference between the peripheral resistance of amputated limbs and those undergoing femorodistal bypass (Mann–Whitney U test, $P=0{\cdot}0001$). Three of the primary amputations had resistances which would have been compatible with reconstruction. No vessels were detected by pre-operative arteriography or conventional Doppler examination but the PGR system demonstrated at least one patent vessel in all three of these limbs.

It was initially thought that the PGR system worked by direct compression of the popliteal and calf arteries. However, satisfactory signals were obtained on diabetic limbs with heavily calcified incompressible vessels. This suggests that compression of the calf muscles was the source, the blood flowing retrogradely into the calf arteries. Patients did not find the pulsatile cuff unduly uncomfortable and no problems of increased ischaemia due to arterial damage were encountered.

Discussion

Conventional pre-operative arteriography may fail to demonstrate patent calf and foot vessels, especially in the presence of severe ischaemia$^{4-6}$. Although distal vessels should be judged to be occluded only if there is filling of the small collaterals, this may not be achieved on the initial arteriograms. It may be uncertain whether failure to demonstrate distal vessels is due to technical factors or due to occlusion. Repeat arteriograms incur additional expense and delay with no guarantee of improved definition. Worse still, it may be assumed that vessels are occluded simply because they have not been filled with contrast medium, and the patient may thus be denied the chance of reconstruction.

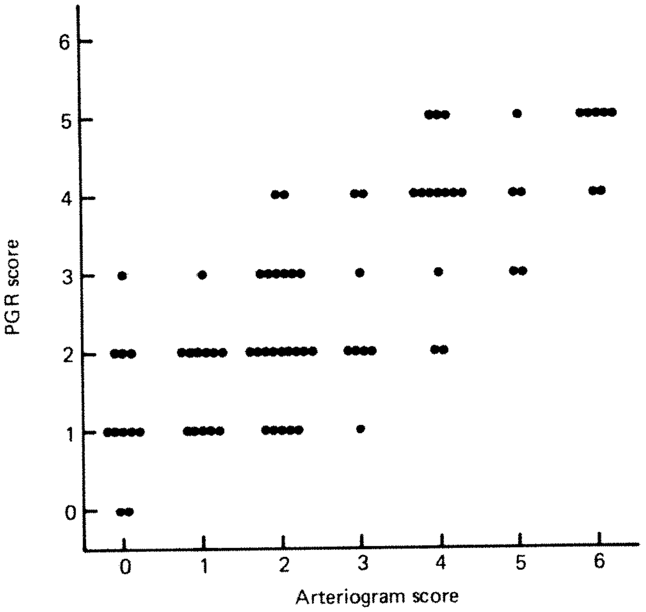

Figure 3 *Pulse-generated runoff (PGR) score against the arteriogram score for the 95 ischaemic limbs (Spearman's rank correlation, 0·74;* P*<0·001)*

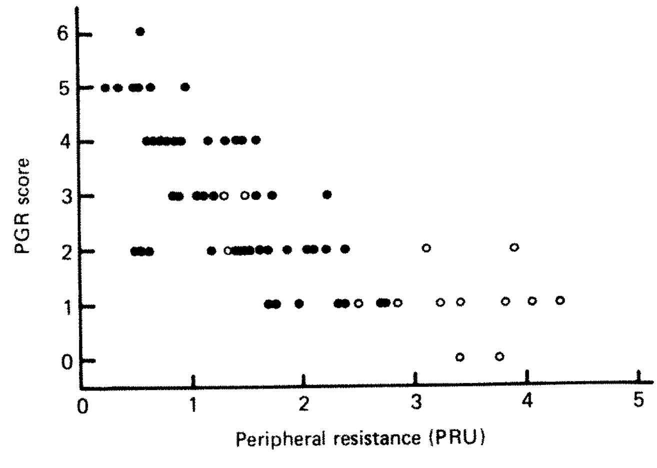

Figure 4 *Pulse-generated runoff (PGR) score against the peripheral resistance for the 62 operated limbs (Spearman's rank correlation, −0·71;* P*<0·001).* ●, *Femorodistal bypass;* ○, *amputation*

An ideal system for assessing distal vessel patency would be non-invasive, safe, simple and rapid to perform. Standard Doppler ultrasound is useful but may also miss patent vessels if signals are severely damped despite a meticulous technique[5]. The addition of the pulse-generated runoff (PGR) system means that the distal vessels can be assessed independently of any proximal disease. Detection of patent vessels in the calf or foot is quickly and easily performed because of the enhanced flow signals.

The PGR system is inexpensive to construct and can be used with any available Doppler velocimeter. PGR correlates significantly with the pre-operative arteriogram score but in severely ischaemic limbs may detect up to 25 per cent more patent vessels. There is a better correlation between the peripheral resistance and PGR than the arteriogram score, suggesting that PGR is a more physiological test of runoff. Pre-operative arteriography usually shows the popliteal and upper calf vessels sufficiently well to indicate the necessary level of bypass. PGR is able to confirm the patency of the distal calf and foot vessels and helps to determine the best vessel for exploration. At present, we feel that the technique augments rather than replaces pre-operative arteriography. A prospective study to assess the predictive value of both methods in determining the outcome of femorodistal bypass grafts is now in progress.

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Dihydroergotamine and the thromboprophylactic effect of dextran 70 in emergency hip surgery

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In a prospective randomized controlled trial treatment with a combination of dextran 70 and dihydroergotamine (DHE) was compared with the administration of dextran 70 alone as prophylaxis against postoperative thrombo-embolic complications in emergency hip surgery. Forty-five consecutive patients with a fractured hip entered the study. Twenty-one were randomized to prophylactic treatment with dextran 70 (group 1) and twenty-four patients received dextran 70 and DHE (group 2). Both regimens were initiated pre-operatively and the surgical and postoperative procedures were the same in the two groups. On the first and fourth postoperative day, Tc-plasmin scintigraphy of the lower extremities and pulmonary ventilation/perfusion scintigraphy were performed to detect any deep vein thrombosis (DVT) and/or pulmonary emboli. A total of 19 per cent of group 1 patients developed DVT and so did 25 per cent in group 2; this difference was not statistically significant. Of the detected DVT, 60 per cent were subclinical, and 7 per cent of the patients had minor pulmonary emboli, all of which were symptomless. No therapeutic difference could be demonstrated between the two regimens. A recent report claiming that adding DHE to the prophylactic administration of dextran 70 considerably reduces the incidence of postoperative DVT in emergency hip surgery is questioned.

Keywords: Dextran, dihydroergotamine, emergency hip surgery, thrombo-embolic prophylaxis

The spontaneous frequency of postoperative deep vein thrombosis (DVT) after emergency operations for hip fractures is $\geqslant 50$ per cent[1], but different methods of prophylactic treatment have been shown to reduce this frequency considerably. After prophylactic administration of dextran 70, the frequency of postoperative DVT has been reported to be about 30 per cent[2,3] and recently it has been found that this incidence could be further reduced to 3 per cent, if a combined treatment with dextran 70 and dihydroergotamine (DHE) was given[3]. This study aimed to reproduce this finding.

Material and methods

As even a reduction in frequency of postoperative DVT from 30 per cent to 10 per cent would represent a major therapeutic advance, this study was designed to demonstrate a reduction of that order if present. The required number of patients to enter the study was calculated according to Clarke and Downie[4]

Forty-six consecutive patients (> 50 years of age) with a fractured hip entered the study. Patients with a previous history of DVT, varicose veins and permanent anticoagulant therapy were excluded before entering the study. One patient was excluded after entering the study, as she died from acute myocardial infarction (verified by autopsy), 20 h postoperatively. All patients had an emergency operation (AO sliding hip screw) within 24 h of hospital admission and were randomized to receive either one of two prophylactic schedules

Group 1 (*dextran prophylaxis*). 500 ml of dextran 70 in 0.88 per cent saline was given on admission to the hospital, during operation, and on the first and third day postoperatively. Patients not mobilized were also given 500 ml on the fifth day.

Group 2 (*dextran+DHE prophylaxis*). Dextran was given as in group 1. DHE (0.5 mg) was injected subcutaneously twice daily starting at premedication as described by Bergquist *et al.*[3] Treatment was continued for 3 days (or 5 days if not mobilized).

Postoperatively all patients followed a routine mobilization and rehabilitation programme, and on the first and fourth days postoperatively Tc-plasmin scintigraphy was performed as described by Gram and Jespersen[5] to detect a DVT. Fixed-point counting was not applied, but a full-leg visualizing technique (gamma camera) was used, and DVT was diagnosed when locally increased activity was observed along the anatomical course of the deep veins. In patients with DVT, perfusion/ventilation scintigraphy of the lungs as described by Kiil and Jensen[6] was done as well. Twenty-one patients entered group 1 and 24 patients group 2. Both groups were comparable regarding age, sex, body weight, operation time and perioperative haemorrhage, and the ratio of operation in general anaesthesia/epidural analgesia was the same in the two groups (*Table 1*).

For statistical analysis Fisher's exact test was used with a 5 per cent significance level. To determine the risk of making a type 2 error, the following formula[7] was used to calculate β

$$C_\beta = \frac{\Delta-(P_1-P_2)}{\sqrt{\frac{1}{N}\left(\frac{P_1(1-P_1)}{K_1}+\frac{P_2(1-P_2)}{K_2}\right)}}$$

with $\Delta = 0.20$ (corresponding to a reduction in the frequency of DVT from 30 per cent to 10 per cent). N is the total number of patients, and K_1 and K_2 the fraction of patients in group 1 and 2. P_1 and P_2 represent the frequency of DVT found in group 1 and 2 respectively

Results

The results are summarized in *Table 2*. DVT was found in four of twenty-one patients (19 per cent) in group 1 (dextran), and in six of twenty-four patients (25 per cent) in group 2 (dextran+DHE). Eight of ten patients with DVT developed this during the first 24 h after surgery, and a further two patients developed DVT between the first and fourth postoperative day. At that time all 45 patients were mobilized except for 4, of whom only one had DVT. None of the demonstrated DVT showed scintigraphical signs of regression between the first and fourth postoperative day, even if anticoagulant treatment had been

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Table 1 *Description of the patients in the two different treatment groups (median and range are indicated)*

	Group 1 (dextran) ($n=21$)	Group 2 (dextran + DHE) ($n=24$)
Sex (F/M)	16/5	20/4
Age (years)	76 (54–90)	78 (50–93)
Weight (kg)	60 (44–84)	59 (40–81)
Duration of operation (min)	60 (35–130)	55 (30–200)
Perioperative haemorrhage (ml)	275 (100–1200)	325 (100–1300)
General anaesthesia/ epidural analgesia	12/9	14/10

Table 2 *Number of patients with scintigraphically proven and clinical signs of deep vein thrombosis and pulmonary emboli*

	Group 1 (dextran) ($n=21$)	Group 2 (dextran + DHE) ($n=24$)
DVT day 1	3	5
DVT day 4	4	6
Symptoms of DVT	2	2
PE	2	1
Symptoms of PE	0	0

DVT, deep vein thrombosis: PE, pulmonary embolus

established since the detection of DVT on the first postoperative day.

In three patients (7 per cent) pulmonary emboli were demonstrated on the perfusion/ventilation scintigraphy. Only four of ten patients with DVT had clinical symptoms and signs (swelling of the calf, tenderness of the deep veins and fever) and all three cases of pulmonary emboli were symptomless, also regarding the concomitant DVT.

No statistically significant difference between the groups could be found. C_β (with $\Delta=0{\cdot}20$) was calculated to be 2·17, corresponding to $0{\cdot}01<\beta<0{\cdot}025$.

Discussion

In this study no further reduction in the frequency of postoperative DVT was found by adding DHE to the prophylactic treatment with dextran 70. This, of course, does not indicate that no difference could possibly exist between the two regimens, but the probability is small (<2·5 per cent) that an existing reduction in the frequency of DVT is as great as from 30 per cent to 10 per cent or more. This suggests that the findings of Bergquist *et al.*[3] from 30 per cent to 3 per cent are incidental. This concept is supported by the fact that Bergquist *et al.* could not demonstrate a similar effect of the same combined treatment on postoperative DVT incidence in elective hip surgery, or in elective or emergency general surgery.

X-ray contrast venography still serves as a reference method for the diagnosis of DVT. However, even when using modified techniques, the method has many disadvantages, especially in emergency patients. In these patients the scintigraphic procedures are more suitable. Tc-plasmin scintigraphy is easy to perform, has a low frequency of adverse reactions and can be applied to seriously ill patients[5]. On the other hand some authors[8] report the specificity of scintigraphy as rather poor and the test is not suitable for detection of pelvic venous thrombosis[5]. However, as this study aimed to reproduce the findings of Bergquist *et al.*[3], we found it important to apply the same methodological set-up to our study as was used in the former. Eighty per cent of DVT were subclinical and symptomless, which is in accordance with other studies[1].

Cost–benefit analysis[9] has shown that it is both of benefit to the patients and financially advantageous to apply thrombosis prophylaxis rather than to apply postoperative routine screening and subsequent treatment of verified cases of DVT. However, it is still questionable whether patients particularly at risk of developing DVT should be postoperatively screened for DVT even when prophylactic treatment has been given.

Patients undergoing hip surgery are known to represent a high-risk category regarding thrombo-embolic complications. In this study all three cases of pulmonary embolus were symptomless, but summarized data from several studies have shown an incidence of postoperative fatal pulmonary embolus of 7·1 per cent without prophylactic treatment and 0·4 per cent with dextran prophylaxis[1]. Many specific, pharmacological prophylactic methods have been used, alone or in combination with general, biomechanical methods and, until now, they have all been shown to have about the same prophylactic effectiveness[2,10–12], although varying degrees of side-effects. Even if orthopaedic patients seem to comprise a specific entity regarding thrombo-embolic complications, it is a general problem that it is impossible to foresee which patients will develop DVT and which patients with DVT will develop fatal pulmonary embolus or troublesome long-term venous complications. For that reason further research in this area is encouraged to develop new and effective prophylactic methods and to find methods to identify pre-operatively those who are particularly at risk of developing pulmonary embolus

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Changes in plasma and buffy layer vitamin C following surgery

Postoperative changes in plasma and buffy layer (BL) vitamin C were studied in 107 patients receiving either 0 (37 patients), 100 mg (33 patients) or 500 mg (37 patients) vitamin C supplements daily. In patients receiving no supplement plasma vitamin C concentrations had fallen (mean 33 per cent) by the first postoperative day and thereafter changed little. The falls occurred irrespective of initial plasma concentration, were greater the higher the initial concentration, but tended to be proportional to the length of operation. In patients given supplements this loss of vitamin C was evident but modified, and from the second postoperative day the response to the supplements was as would have been expected in non-operated subjects. The most probable explanation for the loss of vitamin C from plasma was an increased urinary excretion during operation. Changes in BL vitamin C concentrations were studied in relation to changes in leucocyte and platelet counts. The previously reported postoperative falls in BL vitamin C were found to be the result of a major artefact in the methods routinely used for BL vitamin C estimation, caused by changes in the leucocyte and platelet populations, most importantly the platelet to leucocyte ratio. No true demand for vitamin C, as measured from the buffy layer cells, was evident.

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It is beyond doubt that vitamin C is required for wound healing though its precise role in collagen formation still requires full definition[1–5]. Nevertheless, healing occurs satisfactorily even when nutritional intake is very low[6–8]. Both plasma and buffy layer (BL) vitamin C concentrations fall after surgery and trauma[9–18]. It has also been reported that in some ill postoperative patients, plasma vitamin C concentrations fail to respond to vitamin C supplements[10,12,13]. This has resulted in a wide acceptance that there is a significant demand for vitamin C after surgery and trauma[19] especially as BL vitamin C is considered to reflect tissue vitamin C status[20,21].

However, in one relatively recent study[22] plasma vitamin C concentrations were unaffected by surgery and postoperative falls in BL vitamin C returned to pre-operative values after 1 week, unless patients had received blood transfusions. BL vitamin C measurements have been shown to be significantly affected by the leucocyte count[23–26], though Irvin[17] reported that this did not account for all the postoperative changes in BL vitamin C. More recently it has been shown that the ratio between platelets (largely ignored in most analytical methods for BL vitamin C measurements) and leucocytes—the platelet/leucocyte ratio (PLR)—markedly affects interpretation of BL vitamin C measurement[27]. The present study is a further evaluation of the postoperative changes in both plasma and BL vitamin C, with specific regard to the effect of postoperative changes in leucocyte and platelet numbers on BL vitamin C concentrations. The effect of giving patients different vitamin C (ascorbic acid) supplements is also reported.

Patients and methods

One hundred and seven patients undergoing a wide range of surgical procedures were studied with measurements of plasma and BL vitamin C concentrations along with whole blood leucocyte and platelet counts pre-operatively (on the day of operation), and on each of the first four postoperative days. Further measurements were undertaken on days 7, 10 and 15, and thereafter weekly until discharge from hospital. None of these patients was discharged before day 4 but most left hospital within 2 weeks. Patients were randomly allocated into three groups: one group receiving no supplement (37 patients), and the other two receiving 100 mg (33 patients) or 500 mg (37 patients) of vitamin C daily commencing on the day of operation. There were no significant differences between the groups in relation to age, sex or severity of operations. Supplements were given orally where possible. In patients unable to take oral medication supplements were given intravenously, via an indwelling cannula. They commenced oral supplements as soon as free fluids were tolerated postoperatively. Both oral and intravenous supplements were started on the evening of the day of operation and subsequently given each evening at 6 p.m. The study was approved by the Ethical Committee of the United Birmingham Hospitals. All patients gave their informed consent.

All blood samples collected were either fasting samples or samples taken immediately after breakfast. The hospital diet was devoid of significant sources of vitamin C. Had any been present they would not have affected the results for there is a 1–2 h delay in absorption of vitamin C after ingestion[28–30].

Plasma was separated by centrifugation (3000 rev/min for 10 min) and stabilized in 5 per cent trichloroacetic acid within 1 h of collection from patients. BL separation was performed by a layering technique using a methyl cellulose and sodium diatrizoate solution[31] and samples were stabilized in 5 per cent trichloroacetic acid within 2 h of blood being drawn. Stabilized extracts of both plasma and BL vitamin C were kept at 4°C until analysed. No sample was stored for more than 72 h though such samples are stable for at least 7 days[32]. Analysis for total vitamin C (ascorbic and dehydroascorbic acids) was performed by the method of Marchand and Pelletier[33] twice weekly. BL leucocyte counts were performed on the day of collection using a Coulter Counter model ZX. Whole blood leucocyte counts were performed on a Coulter Counter model S and platelet counts on a Coulter Thrombocounter III (Coulter Electronics Ltd., Harpenden, Hertfordshire, UK).

Statistical analysis of results was performed using the Student's *t* test and the χ^2 test. Variations (including those drawn in the *Figures 1–4*) are given as the standard deviation of the mean.

Results

Changes in both plasma and BL vitamin C concentrations in response to vitamin C supplements were dependent on initial nutritional status. As there was a highly significant correlation between pre-operative plasma and BL vitamin C concentrations ($r = 0{\cdot}953$), the results of patients in each of the three study

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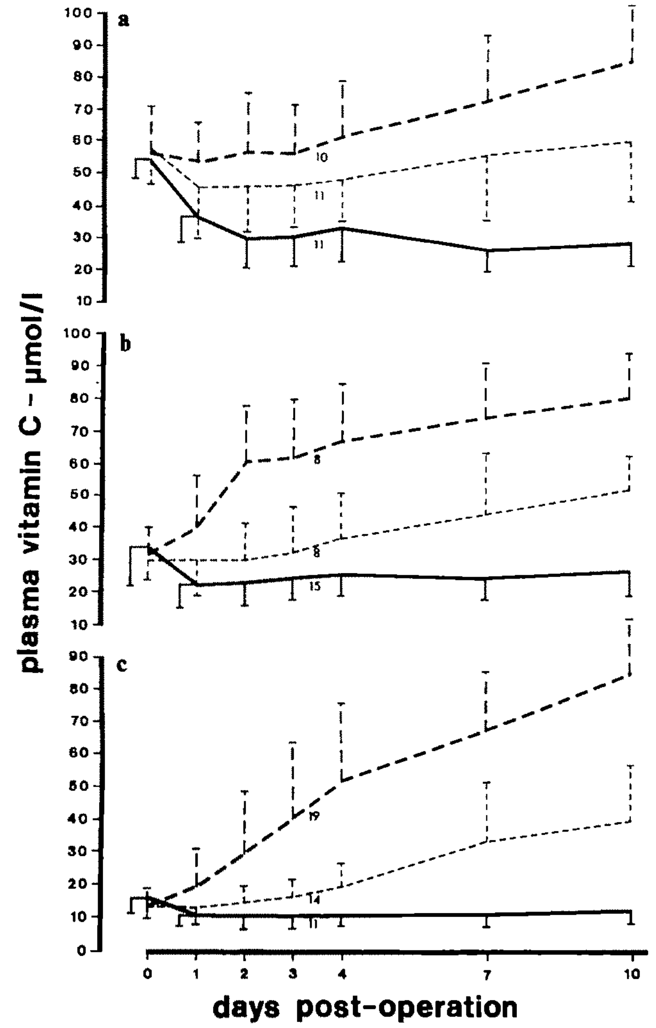

Figure 1 *Changes in plasma vitamin C after surgery.* ——, *Patients who did not receive supplements;* ---, *patients receiving 100 mg vitamin C daily;* — — —, *patients receiving 500 mg vitamin C daily,* **a**, *patients in high subgroups;* **b**, *patients in intermediate subgroups;* **c**, *patients in low subgroups. The numbers along the graphs refer to the number of patients in each subgroup*

groups were divided further into three subgroups depending on whether their pre-operative plasma vitamin C concentration was high (>45 µmol/l, compatible with BL vitamin C saturation[34–38]), intermediate (20–45 µmol/l) or low (<20 µmol/l). The factors affecting changes measured in plasma and BL vitamin C concentrations after surgery were different and are therefore considered separately. The first 10 days' results are displayed in *Figures 1–4*.

Plasma

In the 37 patients who received no vitamin C supplements plasma vitamin C concentrations had fallen by the first postoperative day in all but 2 patients, both with very low pre-operative levels (*Figure 1*). Falls were proportional to the initial plasma concentration and approximately the same (33–36 per cent) in all three subgroups; they were statistically significant ($P<0.001$ high and intermediate subgroups; $P<0.01$ low subgroup). Operations were not timed but falls tended to be least in normally short procedures and greatest in those usually prolonged. Plasma concentrations in most patients with high levels fell further after day 1, and were on average 47 per cent below pre-operative concentrations at discharge (*Figure 1*). In the other subgroups, patients' plasma concentrations showed only minor fluctuations until discharge.

In patients with pre-operatively low or intermediate plasma concentrations the 100 mg supplement largely overcame the fall seen in patients receiving no supplement at day 1 (*Figure 1*), while the 500 mg supplement resulted in increased plasma concentrations. In patients with initially high plasma vitamin C concentrations a fall (not statistically significant) was observed by day 1 in those receiving 100 mg supplement (*Figure 1*) though the mean of the plasma concentration was significantly higher ($P<0.02$) than their 'no supplement' counterparts, while it remained unchanged in those receiving 500 mg. In both 100 and 500 mg groups a number of patients considered suitable for immediate oral therapy were seen to have postoperative falls in plasma concentration similar to those receiving no supplement. All these patients suffered nausea or vomited during the first postoperative day. After day 1 plasma concentrations increased in all subgroups of both supplement groups.

In pre-operatively saturated patients receiving the 100 mg supplement, plasma concentrations had returned to pre-operative levels by the seventh day, while those of patients receiving the 500 mg supplement rose steadily to high concentrations.

In the subsaturated subgroups receiving the 100 mg supplement, plasma concentrations increased steadily to 45 µmol/l by day 7 in the intermediate subgroup and day 10 in the low subgroup. In most subsaturated patients receiving the 500 mg supplement, plasma concentrations had reached 45 µmol/l by day 4 (*Figure 1*).

Seven patients who received supplements (five 100 mg and two 500 mg daily) showed poor absorption of vitamin C on commencing oral supplements (*Table 1*): case 1 suffered a period of acute postoperative renal failure; cases 2–5 underwent gastroduodenal procedures; and cases 6 and 7 were suspected of not taking their oral vitamin supplements as they stated a dislike of the chewable 500 mg tablets. Failure of plasma vitamin C concentrations to respond to supplements was not associated with any delay in discharge from hospital.

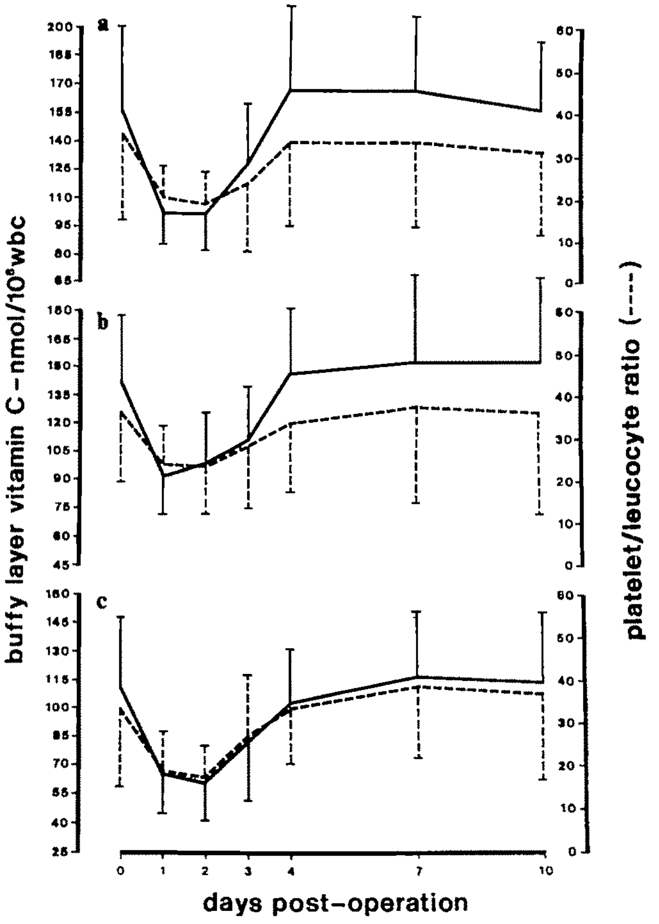

Figure 2 *Changes in buffy layer vitamin C* (——) *and whole blood platelet to leucocyte ratio* (— — —) *after surgery in patients receiving no vitamin C supplements.* **a**, *patients in high subgroup* (n = *11*); **b**, *patients in intermediate subgroup* (n = *15*), **c**, *patients in low subgroup* (n = *11*)

Buffy layer

In patients who received no vitamin C supplements there was a dramatic and highly significant fall ($P < 0·001$) in BL vitamin C by the first postoperative day (*Figure 2*) irrespective of pre-operative concentrations. However, by day 4 it had returned to pre-operative levels in most patients and changed little thereafter. These changes corresponded to the pattern of a highly significant ($P < 0·001$) fall and rise in whole blood PLR. This resulted from a significant ($P < 0·001$) postoperative whole blood leucocytosis which resolved by day 4 while platelet numbers changed little. After day 4 a secondary leucocytosis ($P < 0·01$) and a thrombocytosis ($P < 0·001$) occurred in most patients, though PLR was little affected. BL vitamin C and PLR returned to pre-operative levels coincidentally in all but one patient, who received a 5 unit blood transfusion.

A postoperative fall in BL vitamin C concentration was also found in patients receiving both 100 and 500 mg vitamin C supplements (*Figures 3* and *4*). In pre-operatively saturated patients the pattern of postoperative changes in BL vitamin C was the same as those seen in patients not receiving supplements and corresponded to fluctuations in whole blood PLR, being unaffected by the supplements.

In the subsaturated patients the effects of supplements were evident but were substantially masked by the changes in PLR (*Figures 3* and *4*). In patients in the intermediate and low subgroups receiving 100 mg vitamin C daily the measured falls in BL vitamin C at day 1 were less marked than for patients receiving no supplement, but concentrations had risen above pre-operative values by day 4 (when the PLRs had returned to pre-operative levels). BL saturation was evident by day 7 in most patients in the intermediate subgroup and by day 10 in the low subgroup (*Figure 3*). In most patients in the intermediate and low subgroups receiving 500 mg daily BL vitamin C concentrations had risen above pre-operative levels by day 3,

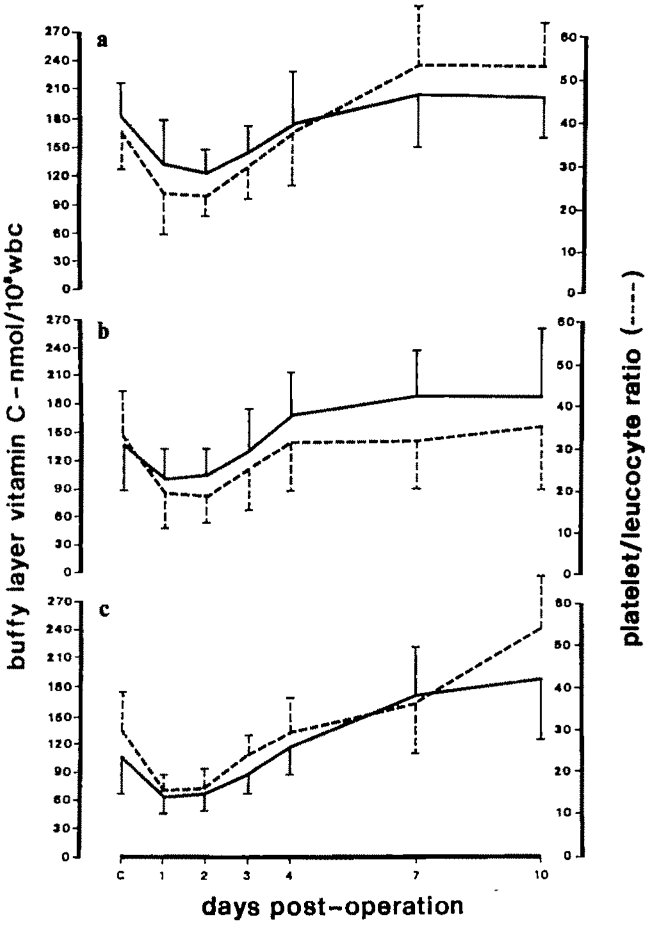

Figure 3 *Changes in buffy layer vitamin C (——) and whole blood platelet to leucocyte ratio (– – –) after surgery in patients receiving 100 mg vitamin C daily.* **a**, *patients in high subgroup* (n = *11*); **b**, *patients in intermediate subgroup* (n = *8*); **c**, *patients in low subgroup* (n = *14*)

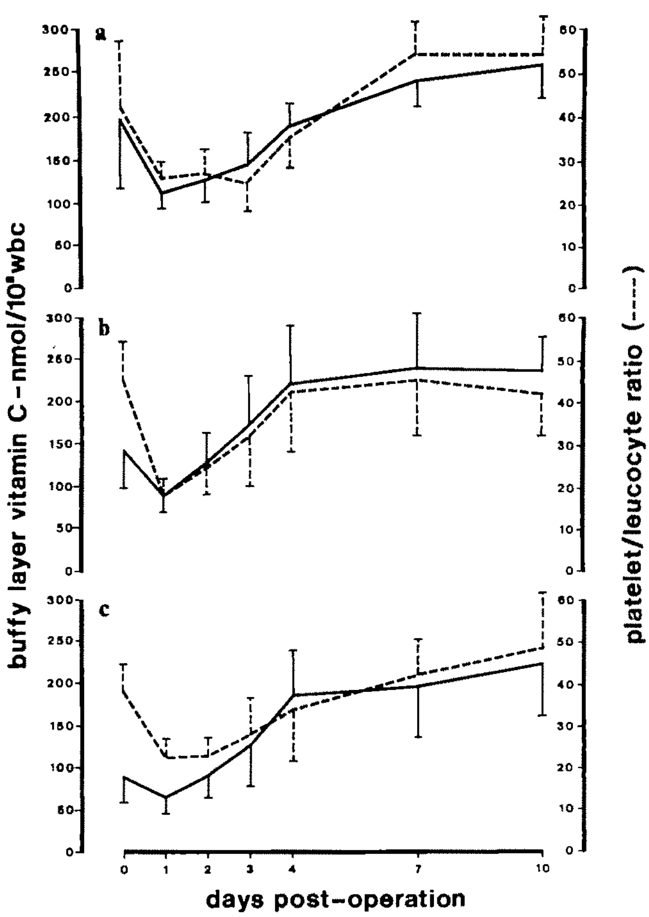

Figure 4 *Changes in buffy layer vitamin C (——) and whole blood platelet to leucocyte ratio (– – –) after surgery in patients receiving 500 mg vitamin C daily.* **a**, *patients in high subgroup* (n = *10*), **b**, *patients in intermediate subgroup* (n = *8*); **c**, *patients in low subgroup* (n = *19*)

Table 1 *Results of patients with poor response of plasma concentrations* (*μmol/l*) *to vitamin C supplements*

				Plasma vitamin C concentration (μmol/l)							
				Postoperative day							
Case	Sex	Ascorbic acid supplement (mg)	Operation	0	1	2	3	4	7	10	15
1	M	100	Aortic aneurysmectomy	15·0	13·8	13·0	—	18·0	19·9†	19·2	26·4
2	F	100	Proximal gastric vagotomy	6·0	6·0	9·0	9·8†	7·8	—	—	—
3	F	100	Proximal gastric vagotomy	50·2	35·5	30·7	30·2†	28·5	—	—	—
4	M	100	Vagotomy and pyloroplasty	28·4	19·2	20·5	23·0	22·5†	21·0	32·0	—
5	M	100	Nissen fundoplication	8·3	8·0	10·0	10·8	15·0	12·5†	15·7	19·8
6	F	500	Cholecystectomy + exploration of the common bile duct	16·7	15·5*	18·3	13·8*	18·8†	15·8	—	—
7	M	500	Left hemicolectomy	16·7	8·0*	8·3*	20·0	38·0	36·9†	31·7	—

* Intravenous supplement not given; † day after oral supplement commenced (previous supplements given intravenously)

when the PLRs were still low (*Figure 4*). By day 4, when PLRs had returned to pre-operative levels, most showed evidence of buffy layer saturation. Once saturation had occurred (mean saturated BL vitamin C concentration being 190 ± 51 nmol/10^8WBC) fluctuations in BL vitamin C were seen only in relation to fluctuations in PLR irrespective of supplement received.

Blood transfusions did not significantly affect the changes in plasma vitamin C concentrations. However, an immediate fall in platelet numbers was noted in the 20 patients who received blood, though this only reached significance in the 9 patients who received 3 or more units of blood (232 ± 65 to $147 \pm 72 \times 10^9$/l, $P < 0{\cdot}05$). Large falls in platelet counts resulted in very low PLRs with correspondingly low BL vitamin C concentrations.

Postoperative complications were few and affected all groups similarly. Hospital stay was shortest in the 'no supplement' group ($7{\cdot}8 \pm 4{\cdot}6$ days against $9{\cdot}7 \pm 7{\cdot}5$ and $10{\cdot}5 \pm 8{\cdot}4$ days for the 100 and 500 mg groups, respectively). Two deaths occurred within 28 days of operation, both in patients receiving supplements. One was a 41-year-old man with chronic renal failure who died suddenly from a myocardial infarct 18 days after undergoing a femoropopliteal by-pass. The other suffered leakage from a gastro-oesophageal anastomosis with fatal sepsis; throughout the postoperative period her plasma and buffy layer concentrations responded normally to the supplements given.

Discussion

Plasma vitamin C analysis in patients receiving no supplement in this study confirmed the falls reported by others, although the fall was greater than the 17 per cent recorded previously[9–15]. Similar percentage reductions in vitamin C concentrations of interstitial fluids would have occurred, as concentration in the two compartments equilibrates rapidly[39]. The absolute loss of vitamin C from both plasma and interstitial fluid would have approached 100 mg in some patients. Significantly these large falls were restricted to the first 24 h after operation, and would have been missed if changes in plasma vitamin C were monitored less closely.

These findings are best explained by the observations of Crandon and associates[13] who reported increased urinary vitamin C excretion during the operative period, suggesting that the renal threshold for vitamin C is reduced during surgical operations, while postoperative urinary vitamin C excretion has been reported as unchanged[14] or reduced[11,40]. This explanation is compatible with the observation that the greatest losses occurred in the longest procedures such as vascular operations on the lower limb (which were not necessarily the most traumatic) and that falls were exponential, tending to be proportional to the pre-operative plasma concentration. A metabolic demand because of surgical trauma would have been expected to be absolute and similar for similar operations, which was not so. A demand because of wound healing would have been expected to continue for many days after surgery in all patients.

The further gradual falls in plasma vitamin C recorded in patients with initially high levels were probably nutritional. Renal vitamin C absorption is never complete[41,42] and postoperatively patients were receiving at best a vitamin C deficient hospital diet[43–45]. Their vitamin C intake would have been inadequate to maintain their plasma levels, while patients with lower concentrations would have required less to maintain their levels[14].

The postoperative changes in BL vitamin C observed in patients receiving no supplement indicated that these were because of changes in the cell populations in the buffy layer, rather than a cellular demand for vitamin C. There is a change not only in PLR, but also in the types of leucocytes present. The postoperative leucocytosis is almost completely caused by an increase in polymorphonuclear cells which have been shown to contain between one-half and one-third of the vitamin C in mononuclear leucocytes[46,47]. Changes in the PLR of BL extracts differ slightly from those recorded from whole blood[27], as used in this study, and explain the slight differences between changes in BL vitamin C and PLR in *Figures 2–4*. Taking this into account, the changes in PLR and leucocyte population accounted for all the postoperative changes in BL vitamin C observed in these 37 patients and have been discussed in detail elsewhere[48]. This is further supported by the observation that changes in BL vitamin C of saturated patients in the supplement groups occurred only in relation to changes in PLR and were not influenced by the supplements given.

As observed in one patient in the present study, McGinn and Hamilton[22] observed that only in patients receiving blood transfusions did the BL vitamin C concentrations fail to recover. This was considered to be because of vitamin C deficient leucocytes in stored blood. However, it is more likely to be attributable to the fall in platelet count which follows transfusion. As plasma and interstitial vitamin C concentrations fall with surgery, subsequent platelet production would take place in an environment containing less vitamin C than pre-operatively. These platelets would be expected to contain less vitamin C than those present pre-operatively, requiring a greater PLR to return BL vitamin C to pre-operative concentrations.

With appreciation of the changes in plasma and BL vitamin C in patients receiving no supplement, the pattern in the two supplement groups was as expected. Once the initial loss of vitamin C from plasma and other fluids had been countered, the supplements increased plasma vitamin C concentrations as in normal subjects. The observation that both plasma and BL vitamin C concentrations of subsaturated patients indicated saturation within 4 days in those receiving 500 mg vitamin C daily and by 10 days in those receiving 100 mg vitamin C daily is compatible with a body pool of vitamin C at saturation of between 1·5 and 2 g[49,50] and no increased demand for vitamin C after surgery. These results contradict the findings of Shukla[16] who reported that in ten young women receiving 500 mg vitamin C daily, plasma concentrations fell persistently until the sixth postoperative day.

The falls in plasma vitamin C concentrations in patients who were considered suitable for immediate oral supplements, but vomited or were nauseated on the night of operation, must have resulted from regurgitation or failed absorption of supplements. Of the seven patients with prolonged failure of vitamin C absorption (*Table 1*), four had undergone gastroduodenal surgery; this association has previously been reported[15,51,52]. No explanation for this has yet been proven, but reduced gastric acidity may affect vitamin C stability after ingestion. The patient with acute renal failure after aortic aneurysmectomy probably developed reduced vitamin C tubular re-absorption with continued inappropriate urinary excretion, for vitamin C concentrations started to increase as his renal failure resolved. The two other cases are explained only by lack of compliance with supplements given, which there was good reason to suspect. The normal response to vitamin supplements of the patient who died after oesophageal resection failed to support previous reports of blood vitamin C concentrations of seriously ill patients not responding to vitamin C supplements[10,12,13].

The number of patients studied here was much too small to determine any benefit from vitamin C supplements. However, nutritionally deficient patients made uncomplicated recoveries from their operations. This would have been expected as the human requirement for vitamin C is small, with a daily intake of 10 mg or less healing the overt signs of scurvy, including wounds[6–8].

In conclusion, surgical operations result in a significant fall in plasma vitamin C, most probably due to an increased urinary excretion of vitamin C. The long-recognized fall in BL vitamin C which follows surgery, previously considered to represent a large demand for vitamin C caused by trauma, appears to be an artefact of the analytical methods used for vitamin C analysis. This would benefit from confirmation using cell separation techniques to allow study of vitamin C concentrations in individual cell types after surgery. The human requirement of vitamin C for wound healing is small and there would appear to be little benefit from giving vitamin C supplements to surgical patients unless they are considered nutritionally very deficient pre-operatively.

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Surgical care of patients over eighty: a predictable crisis at hand

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The number of people over the age of 80 in Britain will increase by around 30 per cent over the next 15 years. Little attention has been paid to the acute surgical services required to meet the surgical needs of this population. This study reviews 198 surgical admissions in 1 year of patients aged 80 years and over, of which 74·9 per cent were admitted as emergencies. The overall mortality was 10·1 per cent of all admissions and 41 per cent of admissions were accompanied by at least one serious complication. Eighty-eight patients underwent surgery with an operative mortality of 11·3 per cent. In only 63·5 per cent of cases could the patient be discharged directly home. By 2001, in Oxford, the proportion of acute surgical beds occupied by patients aged over 80 will increase to 9·2 per cent from the present 7·0 per cent. Unless additional resources are provided to meet this extra demand for acute surgical care of the old, elective surgery for younger patients will inevitably be curtailed.

Keywords: Emergency medical services, health services for the elderly, morbidity, mortality

In 1986, a review by Seymour and Vaz[1] estimated that patients over 75 years of age accounted for 10 per cent of all hospital surgical admissions. In the next two decades, the number of men over the age of 80 in the Oxford region is expected to increase by 35·8 per cent, and the number of women by 24 per cent. The amount of surgical care required by the very old has not been quantified, but is likely to be considerable.

This study was undertaken to provide information on the surgical provision currently required for patients over the age of 80, so that future needs can be predicted.

Patients and methods

All patients aged 80 years and over admitted under the care of the Nuffield Department of Surgery between 1 October 1985 and 30 September 1986 were included in the study, and their case notes were reviewed retrospectively.

The firm is one of four at the John Radcliffe Hospital, Oxford, which is the only hospital accepting acute surgical admissions from a population of 474 000 The Nuffield Department accepted every vascular surgical admission to the hospital during the study period, and was on take for general surgical emergency admissions for 41·9 per cent of the year. A proportion of the hospital's elective general surgical workload was also dealt with by the firm.

A numerical analysis of patients in other age groups admitted during the same period was supplied by the regional statistician, who also provided details of the current catchment population of the hospital, and projected population statistics to the year 2001.

Patients' age, sex, and dates of admission and discharge or death were recorded, in addition to the primary diagnosis on discharge, treatment while in hospital, complications and important co-existing disease. It was also noted whether patients were admitted from home or another institution, and their destination on discharge was recorded.

Results

During the 12 months of the study, 169 patients aged 80 or over were admitted on 198 occasions. Twelve patients were admitted twice, four patients three times, and three patients four times.

General and vascular surgical admissions were recorded separately, as were elective and emergency admissions (*Table 1*).

The median age of the patients was 83 years (range 80–97 years). No seasonal variation in the numbers of admissions was noted for either general or vascular surgical admissions.

Of the 68 vascular surgical admissions, 54·4 per cent were admitted as emergencies. This was the total workload of the hospital in this specialty.

In general surgery, 85·4 per cent of the over-eighties were admitted as emergencies. This is more than the overall emergency general surgical workload as the Nuffield Department of Surgery dealt with a relatively higher proportion of emergency surgery than the hospital as a whole.

Reasons for admission

The causes of general surgical and vascular surgical admissions are shown in *Tables 2* and *3*.

Source of admissions

One hundred and sixty-seven admissions were from home, where the patients lived independently or with varying degrees

Table 1 *Numbers of admissions of patients, aged 80 years and over, in 12 months*

	General surgery		Vascular surgery	
	Male	Female	Male	Female
Emergency	58	53	19	18
Elective	10	9	11	20

Table 2 *Causes of general surgical admissions*

	Numbers of admissions	
Diagnosis	Emergency	Elective
Peptic ulcer disease	8	0
Biliary/pancreatic disease*	7	1
Appendicitis	2	0
Intestinal obstruction†	10	0
Colonic neoplasia	11	7
Diverticular disease	8	0
Abdominal wall hernia	13	6
Gastro-enteritis	6	0
Constipation	5	0
Non-specific abdominal pain	8	0
Other intestinal pathology	8	3
Urological disease	22	1
Miscellaneous	3	1

* One patient was admitted three times as an emergency and once electively with a blockage of an indwelling biliary stent

† Includes one patient admitted on four occasions with recurrent small bowel obstruction due to adhesions

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of support from family, friends or social services. Four patients were admitted from warden controlled accommodation, ten patients were long-term residents in nursing or old patient's homes, and fifteen were in-patients of other hospitals.

The immediate destination on discharge is compared with abode on admission in *Table 4*. Twelve patients were transferred to the care of a urologist, and five patients already being treated by other consultants were returned to their care on the next working day after admission.

Operations performed

Eighty-eight patients underwent surgery (not including angiography or chemical sympathectomy), during the course of their admission. Seven patients underwent two operations and one patient three operations.

There were 11 postoperative deaths after the 97 operations (11 per cent), all but one in-patient operated on as emergencies. Of those patients who underwent surgery, 25 had been admitted electively, and 63 as emergencies. In general surgery, 16 of the 19 patients admitted electively underwent surgery, one was admitted for bowel preparation before sigmoidoscopy, one for endoscopy, and one was considered unsuitable for surgery because of dementia. In vascular surgery, the proportion of electively admitted patients not undergoing surgery was higher, because angiography showed several to be unsuitable for arterial reconstruction.

Details of the operations performed are shown in *Table 5*.

Mortality

Twenty patients died in hospital, an overall mortality rate of 10·1 per cent of admissions. Mortality ranged from nil for patients admitted for elective general surgical procedures, to 21·6 per cent for emergency vascular surgical admissions. Of those patients who underwent surgery, ten died in the immediate postoperative period, although nine of the deaths occurred in patients who had undergone emergency surgery.

Details of all deaths are shown in *Tables 6* and *7* for general and vascular surgical patients respectively.

Eight patients died as a direct consequence of their primary illness. Of the other 12 deaths, chest infection was the primary or major contributory cause in 8 cases.

Table 3 *Causes of vascular surgical admissions*

	Numbers of admissions	
Symptoms and diagnoses	Emergency	Elective
Claudication	0	1
Rest pain	2	11
Critical ischaemia	18	17
Arterial embolism	5	0
Graft thrombosis	2	0
Arterial aneurysm	8	0
Miscellaneous	2	2

Length of stay

The median stay for all patients was 6 days (range 1–51 days). The short median stay of 2 days for elective vascular surgical admissions is accounted for by patients undergoing angiography, angioplasty, and chemical sympathectomy.

Complications

Of the 198 admissions, 59·1 per cent passed uneventfully with no recorded complication. The other 81 admissions experienced 126 complications, the commonest being chest and wound infections, heart failure or cardiac arrhythmia.

Discussion

In 1985, Andrews[2] reviewed the likely changes in the number of old people in the UK over the following 25 years. He expected

Table 5 *Operations performed*

General surgery		Vascular surgery	
Operation	*n*	Operation	*n*
Hernia repair	17	Amputations	14
Laparotomy for:			
Peptic ulcer disease	7	Arterial bypass procedures	9
Colonic disease	14	Embolectomy/thrombectomy	8
Other	11	Aneurysmal disease	4
Miscellaneous	9	Miscellaneous	4

Table 6 *Deaths of general surgical patients*

Age	Primary diagnosis	Treatment	Cause of death
89	Perforated diverticulitis	Hartmann's procedure	Septicaemia
89	Cancer of the pancreas	Symptomatic	Carcinomatosis
82	Clot retention	Catheterized	Myocardial infarction
80	Bleeding duodenal ulcer	Polya gastrectomy	Pulmonary embolism
84	Cholecystitis	Antibiotics	Gastrointestinal bleeding and myocardial infarction
83	Mesenteric infarction	Laparotomy	Mesenteric infarction
82	Bleeding gastric ulcer	Laparotomy and oversewing of ulcer	Renal failure, chest infection and heart failure
81	Appendicitis	Appendicectomy	Pulmonary embolism and heart failure
86	Carcinomatosis	Symptomatic	Carcinomatosis
81	Carcinomatosis	Laparotomy	Carcinomatosis
88	Faecal peritonitis	Symptomatic—surgery declined	Faecal peritonitis

Table 4 *Accommodation of patients at the time of admission compared with destination on discharge*

	Destination (*n*)					
Source (*n*)	Home (108)	Another consultant (17)	Another hospital (31)	Part 3 accommodation (3)	Old people's home/ nursing home (18)	Died (19)
Home (167)	106	17	17	0	9	18
Warden controlled accommodation (4)	0	0	1	3	0	0
Old people's home/nursing home (10)	0	0	1	0	8	1
Another hospital (15)	2	0	12	0	1	0

It was not possible to determine the source of admission or destination on discharge for two patients

Table 7 *Deaths of vascular surgical patients*

Age	Primary diagnosis	Treatment	Cause of death
86	Gangrenous great toe	Angioplasty	Chest infection and heart failure
83	Ischaemic leg	Above knee amputation	Chest infection
81	Ruptured aortic aneurysm	Tube graft and prolonged ventilation	Chest infection and renal failure
87	Gangrenous leg	Angioplasty and femoral thrombectomy	Chest infection
93	Diabetic ischaemic leg	Gritti–Stokes amputation	Renal failure
80	Ruptured aortic aneurysm	Tube graft	Renal failure
90	Gangrenous foot	Symptomatic	Chest infection
96	Ruptured aortic aneurysm	Symptomatic	Ruptured aortic aneurysm
85	Ruptured aortic aneurysm	Symptomatic	Ruptured aortic aneurysm

the total number of people aged 65 years and over to change little, but anticipated a 7 per cent increase in the number aged 75–84 years, and a 34 per cent increase in those 85 years and over. Clarke[3] estimated that by 2001, in England and Wales, there would be a 31 per cent increase in people aged over 75 years, compared with 1981 figures, and a 100 per cent increase in those over 85.

The number of people over 80 in the catchment area of the John Radcliffe Hospital is expected to rise by 27·6 per cent over 15 years, from 11 023 in 1986, to 14 069 by 2001.

Women over 80 currently outnumber men by 2·26 to 1. Over the next 15 years, the ratio of old women to men will decrease throughout the country[4], and in Oxford will fall to 2·06 to 1 by 2001.

In Oxford in 1986, vascular surgical admission rates were 8·9 per 1000 population over 80 per annum for men, and 5·0 per 1000 for women. For emergency general surgery, the rates were 40·8 per 1000 for men, and 16·5 per 1000 for women.

If admission rates are the same in 2001, there will be a 29 per cent increase in all vascular surgical admissions, and a 30 per cent increase in emergency general surgical admissions of patients over 80.

We found a mortality rate of 12·8 per cent in patients admitted as emergencies, compared with 14·5 per cent recorded by Seymour and Pringle[5] in patients over 65 years of age, and 8·6 per cent reported by Stower *et al.*[6] in patients of all ages.

Greenburg *et al.*[7] in their review of gastrointestinal surgery in the elderly concluded that it was sensible to offer early surgical treatment in the elderly, as the probability of complications was increased by delay. Nehme[8] came to the same conclusion for the management of groin hernias, where emergency repair increased the mortality from 1·3 per cent to 7·5 per cent, and the morbidity from 20 per cent to 56 per cent.

The median length of hospital stay in our patients was 6 days, confirming Seymour and Pringle's findings that elderly patients do not, in general, block beds[9]. However, only 63·5 per cent of the patients who had been admitted from home returned there immediately on discharge, and 15·6 per cent were discharged to other hospitals, nursing homes or old people's homes.

This compares favourably with the study by Gilmore *et al.*[10], in which only 751 of 902 patients of all ages admitted to Hackney hospital went directly home, and 12·3 per cent were transferred elsewhere.

Grundy[11] has documented the disproportionate way in which the elderly use hospital resources, and found that patients aged over 85 spent, on average, 12 days a year in hospital, compared with under 1 day for those younger than 50, and just over 2 days for 65-year-olds.

The length of hospital stay has declined for many conditions, but the current vogue for 'day-case' surgery is unlikely to affect the time spent in hospital by the very elderly. Most are admitted as emergencies and the presence of co-existing medical problems makes them unsuitable for 'day-case' operations.

In Oxford, by 2001, an additional 738 hospital days per annum will be spent in caring for general and vascular surgical problems in the over-eighties, if admission rates and length of hospital stay do not change. Assuming that the daily bed occupancy rate is the same as the 1986 figure of 90 per cent, in 2001, the over-eighties will occupy 9·2 per cent of the available acute surgical beds in Oxford, compared with 7·0 per cent at present.

If the provision of health care to younger patients is not to suffer, then either the length of hospital stay for those younger than 80 must decrease still further or more resources must be made available.

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Incisional hernia in re-opened abdominal incisions: an overlooked risk factor

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Many patients undergoing laparotomy will have had a previous incision in the abdominal wall which offers a convenient and logical route for re-exploration. This study aims to examine the risk of subsequent incisional herniation in incisions made through previous scar tissue compared with incisions made through fresh tissues. Out of a total of 1022 laparotomies performed in a 5-year period on one surgical unit, the incisional hernia rates were available for assessment in 699 freshly made incisions, 142 re-incisions and 36 incisional hernias. The incidence of incisional hernia was 6 per cent after freshly made incisions and this incidence was increased after both re-incision (12 per cent, $P<0{\cdot}05$*) and incisional hernia repair (44 per cent,* $P<0{\cdot}01$*). With the exception of jaundice, none of the other commonly accepted risk factors for incisional herniation were significantly increased in those patients with re-incised wounds who subsequently developed a hernia, when compared with patients who did not develop a hernia. An increased risk of incisional herniation is present when laparotomy is performed through a previous abdominal incision.*

Keywords: Incisional hernia, laparotomy, relaparotomy

When faced with the patient who has had a previous abdominal incision, many surgeons will choose to re-incise the abdominal wall through the previous scar, provided that it affords adequate access to the new problems at hand. Apart from the obvious cosmetic considerations, there is also the small risk of skin necrosis between two longitudinally placed scars if these are separated by only a narrow bridge of normal skin. Re-incision would appear the logical choice, but the presence of relatively avascular scar tissue in the wound edges might be expected to impair subsequent wound healing.

The risk of incisional herniation is undoubtedly increased by factors that impair wound healing[1], and these factors help to explain the reported incidence of incisional herniation of between 5 and 11 per cent of abdominal wound closures[2–5]. Our own studies on an earlier cohort of 1129 patients undergoing laparotomy had identified old age, male sex, obesity, wound length, chest infection, abdominal distension, bowel surgery, wound infection and the seniority of the surgeon as significant risk factors associated with incisional herniation[4]. That study did not address the role of re-incision through a previous scar as a risk factor for later incisional herniation and there remains a paucity of information on this subject.

The present study was therefore undertaken to determine whether re-incision may also be considered a risk factor for later incisional herniation. To this end, the incidence of incisional hernia was compared between freshly made incisions and re-incisions performed over a 5-year period. The re-incisions fell into two categories, namely incisional hernia repair and relaparotomy, each of which is considered separately.

Methods

Data have been collected on all of the 1022 patients undergoing elective or emergency laparotomy on one surgical unit during the period 1979–1984. Muscle-splitting appendicectomy incisions were excluded. Midline, conventional paramedian and transverse incisions were used during this time period but all had a common method of wound closure to the rectus sheath with a continuous No. 1 monofilament nylon suture mounted on a large Moynihan-type hand needle. Sutures were placed at least 1 cm from the wound edge and at intervals no greater than 1 cm apart. The length of continuous nylon used to close the rectus sheath was measured routinely, and in all instances the suture length:wound length ratios were greater than 4:1. No deep tension sutures were used and the subcutaneous fat was not sutured. Peritoneal drains were placed through separate stab incisions and no wound drains were used. The length of the wound was routinely measured and the patient's age, sex and build were noted In the immediate postoperative period the presence or absence of abdominal distension, chest infection and wound infection was recorded.

The patients were then followed up at intervals of 1, 3, 6 and 12 months and a specific search was made for incisional hernias. An incisional hernia was defined as a defect in the scar tissue which could be detected by clinical examination. All patients were asked to tense their abdominal muscles by raising first their head and then their legs off the examining couch in order to facilitate detection of any such wound defect.

A total of 145 patients were excluded from analysis because their wounds had not been examined at 6 or 12 months postoperatively; 107 of these patients were known to have died within this first 6 months, the remainder were lost to follow-up. None of the excluded patients had an incisional hernia at the time of their last recorded examination, but as 69 per cent of our hernias were not apparent before the 6-month examination, the data on this group of incompletely followed up patients were considered invalid. Of the remaining 877 patients, 86 per cent were examined at 12 months, 5 per cent died between 6 and 12 months and 9 per cent were lost to follow-up after 6 months. Thus data were available for analysis on 699 freshly made incisions, 142 re-incisions and 36 incisional hernia repairs.

Statistical analysis was by the χ^2 test with Yates' correction and the Mann–Whitney U test.

Results

There was no difference in the age or sex distribution of patients in the three groups, apart from a predominance of males undergoing incisional hernia repair (*Table 1*). There was a higher overall incidence of incisional hernia in both the relaparotomy and the incisional hernia groups compared with the fresh incision group (*Table 2*). Men were more commonly affected than women only in the fresh incision group (*Table 2*).

In the fresh incision and relaparotomy groups the incidence of incisional herniation did not differ significantly between patients undergoing paramedian, midline or transverse incisions (*Table 3*). Midline incisional hernias were more likely to recur than transverse incisional hernias after repair (*Table 3*).

Obesity, jaundice, chest infection, wound infection,

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abdominal distension and wound dehiscence were all identified as risk factors for incisional herniation in the fresh incision group (*Table 4*). With the exception of jaundice in the relaparotomy group, none of these factors was associated with an increased risk of incisional hernia after relaparotomy or incisional hernia repair (*Table 4*). Age was not a significant risk factor in the relaparotomy group, where there was also no difference between the proportions of patients over 65 years with a hernia (35 per cent) and patients with a sound incision (27 per cent).

There was no difference in the percentage of patients undergoing laparotomy for malignant disease between the fresh incision (22 per cent) and the relaparotomy (25 per cent) groups. More relaparotomy patients (53 per cent) underwent bowel surgery than did fresh incision patients (32 per cent), but neither bowel surgery nor malignant disease was a significant risk factor for incisional hernia in this study (*Table 4*).

Table 1 *Age and sex of patients*

	Fresh incision ($n=699$)	Relaparotomy ($n=142$)	Incisional hernia repairs ($n=36$)
Mean age in years (range)	55 (17–85)	55 (19–85)	57 (26–87)
Men (%)	313 (45)	66 (46)	26 (72)
Women (%)	386 (55)	76 (54)	10 (28)*

* $P<0{\cdot}01$, men *versus* women

Table 2 *Incisional hernia rates*

	Fresh incision ($n=699$)	Relaparotomy ($n=142$)	Incisional hernia repairs ($n=36$)
Hernia rate (%)	45 (6)	17 (12)	16 (44)**
Women (%)	4	7	40
Men (%)	9**	18 n.s.	46 n.s.

There was a higher overall incidence of incisional hernia in the relaparotomy group (*$P<0{\cdot}05$) and the incisional hernia group (**$P<0{\cdot}01$) compared with the fresh incision group. There was a statistical difference between men and women in the fresh incision group (**$P<0{\cdot}01$); n.s., not significant

Table 3 *Comparison of incisional hernia rates using paramedian, midline or transverse incisions*

Type of incision	Fresh incision ($n=699$)	Relaparotomy ($n=142$)	Incisional hernia repairs ($n=36$)
Paramedian	21/412 (5)	7/62 (11)	2/7 (29)
Midline	18/189 (9)	9/76 (12)	13/21 (62)
Transverse	6/98 (6)	1/4 (25)	1/8 (12)*

Values in parentheses are percentages. *$P<0{\cdot}05$, midline *versus* transverse

The seniority of the surgeon did not have a significant effect on the incisional hernia rate in either fresh incisions, relaparotomies or incisional hernias. The incidence of incisional hernia after relaparotomy in particular did not differ significantly between consultant (9 per cent), senior registrar (12 per cent) and registrar (15 per cent).

Discussion

Many factors have been implicated in the aetiology of incisional herniation[1]. The present study has identified male sex, obesity, jaundice, chest infection, wound infection, abdominal distension and wound dehiscence as risk factors for incisional hernia in the freshly incised wound. With the exception of jaundice, none of these factors can be implicated as risk factors in the re-incised group. Wound infection, for example, which is an almost universally recognized cause of incisional hernia[3,6,7], was no more common in re-incised patients who developed a hernia than in those who did not. Bowel surgery was performed more often in the re-incised group and was certainly a risk factor in our own earlier study of a previous cohort of 1129 patients[4], but in the present study was found not to be a risk factor for either fresh or re-incised wounds. It is not clear whether this change in bowel surgery as a risk factor is the result of altered surgical or prophylactic antibiotic policy in the 10-year period which the two studies span, but the pitfalls of comparison with historical data are well recognized.

Age, wound length and seniority of the surgeon also failed to appear as risk factors in the present study whereas they had been significant in our previous study[4]. A further difference is the presence of jaundice as a risk factor in the current study. Experimental evidence suggests that obstructive jaundice decreases the strength of abdominal wound healing and delays fibroplasia and angiogenesis[8]. These findings have been confirmed clinically to result in a higher incidence of both wound dehiscence and incisional hernia in patients with obstructive jaundice[9], consistent with the findings in our present study.

Re-incision of the abdominal wall through scar tissue has not previously been evaluated by either ourselves or, to our knowledge, other authors as a risk factor for incisional hernia. While many surgeons excise the cutaneous scar tissue when re-incising an abdominal wound, the deeper fascial layers are not usually excised, leaving two opposing surfaces of relatively avascular scar tissue in the deeper layers of the wound. Satisfactory healing of these deeper layers is essential to the subsequent integrity of the wound. Any impairment of this healing, such as may occur in scar tissue, might be expected to increase the incidence of incisional herniation.

With the exception of jaundice, which accounted for 23 per cent of the patients who developed incisional hernias, no

Table 4 *Incidence of risk factors for incisional herniation*

	Fresh incision		Relaparotomy		Incisional hernia repairs	
Risk factors	No hernia ($n=654$)	Hernia ($n=45$)	No hernia ($n=125$)	Hernia ($n=17$)	No hernia ($n=20$)	Hernia ($n=16$)
Mean age (years)	55	58	54	61	57	58
Obesity (%)	23	40*	14	0	50	38
Wound length > 18 cm (%)	57	58	70	76	65	56
Malignant disease (%)	23	11	27	6	—	—
Bowel surgery (%)	32	29	54	41	—	—
Jaundice (%)	4	13**	4	23**	0	0
Chest infection (%)	16	36**	18	24	15	19
Wound infection (%)	15	49**	13	18	10	25
Distension (%)	12	29**	20	23	5	19
Dehiscence (%)	0·5	11**	0	0	0	6

*$P<0{\cdot}02$, ** $<0{\cdot}01$, hernia *versus* no hernia

other risk factors could be implicated as a cause of the increased rate of incisional hernia in re-incised wounds. This finding suggests that there is an inherent defect in the re-incised wound itself that encourages subsequent incisional herniation, which is unrelated to either the type of surgery or the incidence of complications occurring in the patient who undergoes surgery through previous scar tissue. Clearly further experimental work is required to validate this hypothesis, but it is interesting to note that no identifiable risk factors were present in the incisional hernia group either. The incidence of wound infection in incisional hernias which recurred, however, was over twice that of sound repairs, and although this difference was not significant, the numbers involved were small. In a larger study of 81 incisional hernias, including some of these patients, we did, in fact, find that wound infection was a significant risk factor[10].

Tension on the suture line was not measured in this study, but may account for the difference in hernia rates between incisional hernias (44 per cent) and re-incised wounds (12 per cent). Indeed we no longer use direct suture to repair incisional hernias, preferring instead to use Marlex or GORE-TEX (W. L. Gore and Associates Inc.) patches sutured without tension. It is still too early to say what effect this new policy has had on recurrence rates after incisional hernia repair, but other series note an incidence of recurrent hernia of only 6–11 per cent using Marlex patches[11,12].

This study has demonstrated an increased risk of incisional hernia in re-incised abdominal wounds. Clearly these wounds are already closed by conventional means with a considerable degree of care, as witnessed by the absence of wound dehiscence in any of the re-incised patients. Nevertheless further work is needed to identify a more effective means of repairing such wounds which will provide them with better long-term integrity, and allow us to approach the 1 per cent incidence of incisional herniation currently being achieved with the lateral paramedian incision in freshly incised wounds[13]. Indeed, we have now modified our technique of re-incised wound closure, and are currently using interrupted near and far Smead-Jones sutures[14] in a wound trial setting, both to determine the effectiveness of this technique in reducing subsequent incisional herniation and to compare the value of nylon and Novafil as closure materials for the re-incised rectus sheath.

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Consequences of blood loss on growth of artificial metastases

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Previous studies have shown that lung metastases from a non-immunogenic sarcoma (LS175) in BN (homozygous for $RT1^n$) rats were stimulated by blood transfusions. Enhanced growth was also observed after abdominal surgery combined with allogeneic blood transfusions while syngeneic blood transfusions had no effect. These experimental findings have been confirmed in retrospective clinical studies. The allogeneic blood transfusion effect may be avoided in cancer patients by autologous blood transfusions although this implies blood donation before surgery. The aim of the present study was to investigate the effect of blood loss before surgery on formation ('take') of lung colonies, and on the outgrowth of established metastases in the BN rat model. These aspects of tumour behaviour were also investigated in rats undergoing surgery, or receiving blood transfusion, or both, after blood loss. The results indicate that blood loss has a profound stimulating effect on the growth of established metastases, but not on the 'take' of tumour cells. This stimulating effect was also present when blood loss was combined with surgery, while previously surgery alone was found to have no effect. Allogeneic and syngeneic transfusions in combination with blood loss both had a strong stimulating effect on growth of established lung metastases. The results indicate that blood loss may be an important factor in determining the outcome of metastatic growth.

Keywords: Blood loss, blood transfusions, surgery, tumour

Blood transfusions appear to have numerous consequences which were never envisaged at the time of their introduction. Despite careful blood donor screening, a substantial number of patients receiving transfusions have serious adverse effects such as serum hepatitis, acquired immune deficiency syndrome, and sensitization to foreign antigens. A well-recognized beneficial effect is the longer survival of kidney grafts in recipients given blood transfusions before transplantation, a finding confirmed in various animal models[1–3]. There is no consensus concerning the mechanism(s) responsible for this phenomenon, but some form of modulation of the host's immune response by blood transfusions has generally been implicated, i.e. induction of suppressor cells, anti-idiotypic antibodies and non-specific immunosuppression[4–6]. Recent clinical retrospective studies have demonstrated an association between perioperative blood transfusions and tumour recurrence in surgically treated patients[7–10]. These findings have also received support from the results of experimental work by Francis and Shenton[11] and by ourselves in rats where we have demonstrated a promoting effect of blood transfusion on the growth of artificial metastases[12].

Several disorders in the immune system have been reported after surgical trauma. Riddle and Berenbaum[13] have shown a decline in lymphocyte response to phytohaemagglutinin in postoperative patients. Constantian *et al.*[14] demonstrated the presence of an endogenous immunosuppressive polypeptide in the serum of traumatized patients. Slade *et al.*[15] have demonstrated a decrease in a multitude of immune parameters measured *in vivo* and *in vitro* in normal patients after nephrectomy. In the treatment of cancer patients, very often the only curative treatment is surgical resection of the primary tumour. It is often an extensive surgical procedure with profound blood loss for which subsequent blood transfusions is indicated. The results mentioned above regarding immunomodulation after blood transfusions and surgery, together with the retrospective data indicating a decreased survival rate of surgical patients receiving blood transfusions, have potentially grave consequences for cancer patients.

A possible solution would be to reduce the need for allogeneic blood transfusions, and thus avoid the subsequent effects on the patients' immune apparatus. The use of autologous blood transfusion would circumvent this hazard. This would involve collecting autologous blood before surgery and the technical feasibility of this procedure has previously been demonstrated[16–17]. The consequences for the immune status of cancer patients of pre- and peroperative blood loss have not yet been investigated.

In the present communication we report the effects of blood loss, surgery, and subsequent blood transfusions on the growth of established artificial tumour metastases in a rat model Furthermore, the effect of blood loss alone and in combination with blood transfusions on the 'take' of tumour cells was studied, as this might be of consequence for the tumour cells released in patients by tumour manipulation during surgery.

Materials and methods

Animals

Male rats of the inbred BN and WAG (homozygous for $RT1^u$) strains were used. .The animals were bred under specific pathogen-free conditions and were 16–20 weeks old.

Tumour

Tumour LS175 is a spontaneous, non-immunogenic sarcoma in BN rats The tumour is maintained as a stationary culture in Dulbecco's minimum essential medium, supplemented with 10 per cent fetal calf serum. To obtain cells for the *in vitro* experiments, free floating LS175 cell clumps were harvested from the tissue culture flasks and, after washing, were resuspended in Hank's balanced salt solution Single cells were prepared by rinsing the suspension through a pipette. Viability was assessed by Trypan Blue exclusion and was usually between 90 and 95 per cent.

Lung colonies assay

A total of 2.5×10^5 tumour cells, suspended in a volume of 1 ml, were injected intravenously into experimental and control rats. The numbers

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Table 1 *Effect of blood loss and blood transfusions on 'take' of tumour cells*

Tumour cells given intravenously on day 0	Number of animals	Number of lung colonies (mean ± s.d.)	P
Control	10	17±6	
Bled on day −7	8	20±7	0·2
Bled on day −7 + syngeneic transfusion on day 0	7	18±2	0·4
Bled on day −7 + allogeneic transfusion on day 0	7	20±4	0·2

Experimental groups are compared with the control group Limit of significance $P \leqslant 0·01$

of colonies developing in the lungs were counted after 27 days. The lungs were excised, rinsed in tap water and subsequently fixed in Bouin's solution. Tumour nodules on the lung surface, visible to the naked eye, were counted.

Blood transfusions

BN rats received a single intravenous injection of 1 ml heparinized whole WAG blood or 1 ml of syngeneic blood. Control animals received no transfusions

Blood loss

BN rats were bled a volume of 4 ml blood by means of a tail incision. This volume represents approximately 30 per cent of the total blood volume of the rats used.

Abdominal surgery

Under ether anaesthesia a length of 5–6 cm of ileum was resected and subsequently re-anastomosed using a continuous suture of 7·0 silk. The procedure lasted 15–20 min, with an estimated blood loss of c. 2 ml.

Experimental design

To investigate the effect on 'take' of tumour cells, animals were bled 7 days before tumour cell inoculation and subsequently given allogeneic or syngeneic blood transfusions on the day of tumour inoculation. To study the effect on 'growth' of established lung metastases animals were bled 7 days after the tumour cell inoculation. On day +14 animals received syngeneic or allogeneic blood transfusions alone or in combination with abdominal surgery. One group underwent abdominal surgery but received no transfusion. Control animals received tumour cells on day 0 and received no further treatment. Each experimental group contained 6–13 animals.

Statistical analysis

All data were analysed by two-way testing according to the Mann–Whitney *U* test when comparing two groups, and the Kruskal–Wallis test was employed for simultaneous comparison of more than two groups The experimental error rate was reduced by using the significance level of $P < 0·01$[18].

Results

Effect of blood loss and blood transfusions on 'take' of tumour cells

BN rats were bled 7 days before tumour cell inoculation. On the day of tumour inoculation the experimental groups were transfused with 1 ml syngeneic or allogeneic blood or received no transfusion at all. The control group was not bled and received no transfusion. The lung colonies were counted on day 27 after tumour injection. The mean number of colonies ranged in different groups from 17 to 20 nodules, with a substantial standard deviation, as shown in *Table 1*. No significant difference in the number of colonies was found in groups bled whether or not they received blood transfusions, as compared with the control group. These results indicate that blood loss on day −7, and subsequent administration of blood transfusions on day 0, had no significant effect on the 'take' of tumour cells.

Effects of blood loss and subsequent blood transfusions on growth of established lung metastases

BN rats were inoculated with tumour cells on day 0 and bled on day +7. Two groups received allogeneic or syngeneic blood transfusions respectively, on day +14. The control group was inoculated with tumour cells, was not bled and did not receive blood transfusions. The mean (±s.d.) number of lung colonies in the control group was 15±11 while that of the group bled on day +7 was 79±54 (*Table 2*) ($P < 0·0003$). The mean (±s.d.) number of colonies in the groups which were bled on day +7 and which subsequently received syngeneic or allogeneic blood transfusions on day +14 were 60±50 and 120±50, respectively. In spite of the large standard deviations, the number of colonies in both groups was significantly higher than in the control group ($P < 0·005$ and $P < 0·0001$, respectively). There was no statistically significant difference between the three experimental groups. These results indicate a substantial stimulation of growth of established lung metastases after blood loss.

Effects of bleeding, abdominal surgery and blood transfusions on growth of lung metastases

BN rats injected with tumour cells on day 0 were bled on day +7. On day +14 groups underwent procedures as shown in *Table 3*: they received syngeneic or allogeneic blood transfusions, or underwent abdominal surgery, with or without additional blood transfusion. The control group were only inoculated with tumour cells on day 0. The results are given in

Table 2 *Effect of blood loss and blood transfusion on growth of lung metastases*

Tumour cells given intravenously on day 0	Number of animals	Number of lung colonies (mean ± s.d.)	P*
Control	13	15±11	
Bled on day +7	7	79±54	0·0003
Bled on day +7 + syngeneic blood transfusion on day +14	8	60±50	0·005
Bled on day +7 + allogeneic blood transfusion on day +14	7	120±50	0·0001

Experimental groups are compared statistically with the control group. Limit of significance $P \leqslant 0·01$

Table 3 *Effect of blood loss, abdominal surgery and blood transfusions on growth of metastases*

Tumour cells given intravenously on day 0	Number of animals	Number of lung colonies (mean ± s.d.)	P*
Control	11	41±12	
Bled on day +7	6	219±43	0·0002
Bled on day +7 + syngeneic transfusion on day +14	6	158±28	0·0002
Bled on +7 + allogeneic transfusion on day +14	6	261±47	0·0002
Bled on day +7 + abdominal surgery on day +14	6	76±26	0·003
Bled on day +7 + abdominal surgery + syngeneic transfusion on day +14	6	135±53	0·0003
Bled on day +7 + abdominal surgery + allogeneic transfusion on day +14	6	179±50	0·0002

Experimental groups are compared statistically with the control group. Limit of significance $P \leqslant 0·01$

Table 3. The groups which were bled only or additionally received syngeneic or allogeneic blood transfusions showed a significantly higher number of lung colonies when compared with the control group ($P<0.0002$). This is in accordance with the results shown in *Table 2*. Furthermore, the number of colonies were significantly higher in the group receiving allogeneic transfusions than in the groups which had only been transfused with syngeneic blood or had only been bled. This illustrates the detrimental effect of blood transfusion superimposed on the effect of blood loss. The mean number of colonies in the group bled on day +7 and undergoing abdominal surgery on day +14 was 76±26, which is significantly higher than the mean of the control group, 41±12 ($P<0.003$). The groups bled, undergoing abdominal surgery and additionally receiving syngeneic or allogeneic blood transfusions had a mean number of colonies of 135±53 and 179±50, respectively, which is significantly higher than the control group. These results demonstrate stimulation of growth of lung metastases after blood loss alone, or in combination with blood transfusions and/or abdominal surgery.

Discussion

Abraham and Chang[19,20] have reported profound depression of inflammatory response and decreased mitogenic induced lymphocyte proliferation after haemorrhage. Loegering and Carr[21] have reported deficiency of circulating opsonic activity and reticulo-endothelial system depression during haemorrhagic shock. Susceptibility of patients to sepsis after trauma and haemorrhage is well recognized clinically[22] Bleeding the cancer patients before surgery would be a prerequisite for autologous blood transfusion. Considering the reports above, this prerequisite could have consequences for the 'take' of tumour cells released during manipulation of the primary tumour during surgery. However, the data in *Table 1* show that blood loss on day −7 did not have an effect on the 'take' of tumour cells on day 0. Subsequent syngeneic or allogeneic blood transfusions after blood loss also had no effect on 'take'. In this tumour model we have previously shown[12] that blood transfusions on day −7 had no effect on 'take' of tumour cells. A possible explanation could be that in the process of 'take', factors other than the immune status are of greater importance. These could be coagulation status at the time of tumour inoculation and inter-tumour cell interaction. The data presented in *Table 2* demonstrate a stimulating effect of blood loss on the growth of established metastases. We have shown previously[12] that syngeneic blood transfusion does not affect the growth of established lung metastases in this tumour model. The present results show a stimulating effect in the group receiving syngeneic blood transfusion when combined with prior blood loss and in the group with blood loss only. This indicates an overwhelming adverse effect of blood loss. The group which was given allogeneic blood also showed greatly enhanced growth of lung colonies, and these results are confirmed by the results in *Table 3*. Hattari *et al.*[23] have demonstrated enhancing effects on tumour growth and Jubert *et al.*[24] have shown impairment of immunocompetence, after peroperative blood loss. Our results show a similar trend: an enhancing effect on tumour growth is observed in groups undergoing abdominal surgery and additionally receiving allogeneic or syngeneic blood transfusions, preceeded by blood loss on day +7. An explanation for the discrepancy between the effects of blood loss on 'take' and growth of established metastases could be the importance of different factors exhibiting a prominent role in the different phases of tumour kinetics. The assumed immunosuppression produced by blood loss, blood transfusions and surgery might be responsible for the enhanced growth of metastases; while other factors, as stated above, play an important role in the outcome of 'take' of tumour cells. These results stress the need for further investigations of immunoparameters after a period of blood loss.

The prerequisite for any autologous blood transfusion, i.e. blood loss before surgery, may have serious consequences for cancer patients undergoing surgical treatment.

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Fine needle aspiration cytology: an in vitro study of cell yield

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To investigate the effect of needle size and number of passes into a tumour mass on the cell yield from a fine needle aspirate, an in vitro *study was undertaken in 19 consecutive tumours removed surgically for biopsy. Different needle sizes (23G, 21G, 19G) passed in random order, five, ten and fifteen times into the tumours, were compared. The type of tumour, needle size and number of passes independently and significantly influenced cell yield. A 21G(green) needle passed into the tumour at least 10 times was the most efficient in obtaining cells. This* in vitro *study could explain the variation in the reported accuracy of fine needle aspiration cytology from groups using different techniques and is perhaps one reason why the highest diagnostic accuracy and the lowest rate of unsatisfactory aspirates comes from a centre which uses a 21G needle and at least 10 passes through the tumour.*

Keywords: Fine needle aspiration cytology, cell yield

Fine needle aspiration cytology (FNAC) is a valuable technique in the pre-operative diagnosis of solid tumours. It relies on obtaining sufficient cells representative of the tumour and skilful interpretation of these cells by a trained cytologist. However, up to 48 per cent of all aspirates can be unsatisfactory[1]. An unsatisfactory aspirate is one with either few or no representative cells (acellular) or cellular material which is damaged, necrotic, blood-stained or poorly fixed making interpretation difficult. Differences in technique may account for this. In particular different gauge needles have been used, e.g. 23G, 22G, 21G and 19G[2–6], with variable numbers of passes into the tumour from two up to fifteen[1,7–9]. The purpose of this study was to observe the effect of needle size and the number of passes into the tumour on cell yield because poor cell yield has been suggested as a cause for unsatisfactory aspirates[3].

Materials and methods

A consecutive series of 19 specimens (13 malignant and 4 benign breast tumours and 2 malignant lymph nodes) removed at operation were studied within 1 h of removal.

With each of three different gauge needles (23G, 21G and 19G), five, ten and fifteen passes were made into each specimen, in random order, using the technique of Dixon *et al.*[1] by a single operator (M.H). A 10 ml syringe was used, it was hand held and the needle introduced into the tumour which was held steady with the other hand. Suction was then applied pulling the plunger back to the 5 ml mark and then the needle was passed into the tumour the appropriate number of times without losing suction The plunger was then allowed to return to the zero mark before withdrawal. Each of the nine aspirates was then flushed into 10 ml of cytospin collection fluid (Shandon Southern Products Ltd) and cytospin preparations made. Each 10 ml suspension was spun at 10 000 r.p.m. for 10 min and the deposit resuspended in 2 ml of saline Then 0·5 ml of this suspension was spun at 1500 r.p.m. for 3 min in a cytospin sample chamber The cells were fixed in alcohol and stained with Papanicolaou stain on glass slides which were then independently coded.

The cells in the centre low power field (× 10) of each cytospin were counted. After decoding, the cell counts were then matched for needle size and number of passes

Analysis of the data was by two-way analysis of variance and Tukey's studentized range test for multiple comparisons (Statistical Analysis System package, SAS Institute Inc., N.C. 27511, USA).

Results

Thirteen malignant and four benign breast tumours and two malignant lymph nodes were studied. Of the breast lumps: seven were poorly differentiated ductal carcinomas; four were invasive ductal carcinomas; two were poorly differentiated lobular carcinomas; and four were fibroadenomas. Six of the malignant breast tumours showed scirrhous features. Of the lymph nodes one contained metastatic breast carcinoma and one contained metastatic squamous cell carcinoma. No tumour was $<0{\cdot}01$ dl.

Table 1 shows the mean counts for each needle size and number of passes in 19 tumours. The count distributions were positively skewed and therefore subjected to square root transformation to obtain a better normal probability plot.

Table 2 shows that the variables—tumour, needle size and number of passes—had independent and significant effects on cell yield but not needle size and number of passes combined.

There was no significant difference in cell yield between a 19G and a 21G needle but each yielded significantly more cells than a 23G needle ($P<0{\cdot}05$). There was no significant difference in cell yield between 10 and 15 passes but each yielded more cells than 5 passes ($P<0{\cdot}05$).

Table 1 *Mean (s.e.m.) counts for each needle size and number of passes*

	Number of passes		
Needle size	5	10	15
23G	683 (117)	929 (221)	1237 (309)
21G	1103 (300)	1620 (370)	1608 (228)
19G	1154 (271)	1630 (363)	1899 (323)

Table 2 *Two-way analysis of variance on four variables*

Source of variation	d.f.	F-value	*P*
Tumour	18	12·14	0·0001
Size	2	10·41	0·0001
Passes	2	11·09	0·0001
Size/passes	4	0·29	0·88

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Discussion

The results show that the type of tumour significantly influences cell yield when performing FNAC but the size of the needle and the number of passes into the tumour also have significant independent effects.

These data suggest that in clinical use a 21G (green) needle with 10 passes into the tumour should achieve a significantly better cell yield. There appears to be no advantage in using a bigger gauge needle (19G) or increasing the number of passes to 15.

Clinically it is skin puncture which is painful; a 21G rather than a 19G is therefore more comfortable and increasing the number of passes from five to ten does not appear to create further discomfort as the skin is only punctured once.

These results support the clinical studies of Dixon *et al.*[1,10]. They obtained only 1 per cent unsatisfactory smears using FNAC in the diagnosis of 516 breast carcinomas by a single operator using a 21G needle and a 10 ml syringe with at least 10 passes into the tumour. In their study emphasis was placed on the single operator with aptitude for the technique as the main factor in obtaining good results but we have shown that the technique itself is important to obtain the most representative material for the cytologist.

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Operative treatment of median cervical cysts

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Median cervical cysts are congenital anomalies arising from remaining thyroglossal duct epithelium. A major problem in the surgical treatment of these cysts is the high frequency of recurrence. Embryonic considerations indicate an important causal role for the hyoid bone in these recurrences. We studied the relationship between operative techniques and the number of recurrences in 36 patients treated in our hospital. Fourteen patients sent from other hospitals had a recurrent fistula; in thirteen cases the hyoid bone was still in place. All patients who had the central part of the hyoid bone excised were cured. In 14 patients without adequate excisions of the hyoid bone we found four recurrences. To prevent recurrence a total excision of thyroglossal duct epithelium is necessary.

Keywords: Recurrent thyroglossal duct cysts, median cervical cysts

A median cervical cyst is a congenital anomaly that arises from an epithelial remnant of the thyroglossal duct. This is an embryonic structure which develops in close relationship with the thyroid gland, out of an ectodermal proliferation between the first and second pharyngeal pouch[1–3]. As a result of embryonic growth and development, the thyroid gland migrates downward, via the paired primordium of the hyoid bone, to its final location.

The thyroglossal duct connects the thyroid gland with the foramen caecum and has a close relationship with the hyoid bone. Normally, this duct obliterates and atrophies between the sixth and ninth week[1–5]. If, however, epithelial tissue remains cysts can develop, which consequently are situated in the midline of the neck[3,6]. Most median cervical cysts (65 per cent) are located caudal from the hyoid bone, 15 per cent of the cysts occur at the level of the hyoid, and 20 per cent are found in a suprahyoid position[3].

Surgical excision of the cysts is the therapy of choice. However, the high frequency of recurrence is a major problem. Radical excision of duct-epithelium is a prerequisite in the prevention of these recurrences[3,8,9].

In a retrospective case-control study we investigated the relationship between the operation used and the number of recurrences.

Patients and methods

Between 1972 and 1986, 36 patients (male 19; female 17) with median cervical cysts were operated on in the University Hospital Dijkzigt, Rotterdam. The mean age was 32·5 years, with a range from 7 to 75 years. Twenty-two patients had a primary operation; fourteen patients sent from other hospitals had a recurrent cervical fistula, varying between the first and eleventh recurrence.

The number of children in this group is relatively small, because they are virtually all operated in the children's hospital. These children were not included in this study

Operations were performed according to the technique described by Sistrunk[8]. The patient is positioned with the neck in hyperextension. A transverse incision over a cyst is made; in patients with a fistula, methylene blue is injected in the fistula and an ellipse of skin around this fistula is included in the incision. By sharp and blunt dissection the cyst is withdrawn from its surroundings; a tract or fistula surrounded by a longitudinal block of tissue is dissected upwards to the hyoid bone. Upper and lower margins of the hyoid are bared from the attached muscles; the central part of the hyoid bone is cut and included in the excision. This segment is left attached to the tract or fistula. In tracing the tract into the suprahyoid region and toward the foramen caecum, the excision will include a part of the mylohyoid, geniohyoid and genioglossus muscles. The cyst, hyoid bone and attached tract are then excised *en bloc*.

Results

The symptoms with which the patients presented are mentioned in *Table 1*. A swelling was seen in 21 patients; 7 patients had a fistula, 8 patients had a combination of a swelling and a fistula. Fourteen of 29 cysts were localized distally from the hyoid bone. In 15 patients, the cyst occurred at the level of the hyoid bone, or in a suprahyoid position. In varying numbers, additional diagnostic investigations were performed (*Table 2*). To exclude ectopic thyroid tissue or agenesis of the thyroid gland, a scintigram was made in 14 patients. All scintigrams were normal.

Operative findings are shown in *Table 3*. In 11 patients with a recurrent fistula, the hyoid bone was still in place; in 2 patients a remnant of the hyoid bone was found. In one patient the hyoid bone was removed in an earlier operation.

In 21 patients the central part of the hyoid bone was included in our excision of duct epithelium. However, in three patients an inadequate excision was done (only cleavage of the hyoid bone), and in eleven patients the hyoid bone was left undisturbed ($n = 14$, 39 per cent).

At histological examination ectopic thyroid tissue was found in six patients (17 per cent). None of our patients had a carcinoma. In our follow-up varying between 3 weeks and 10 years, we found four recurrences, which all developed within 16

Table 1 *Presenting symptoms of patients with midline cysts*

	No. of patients
Infection and drainage	13
Growth of a swelling	8
Disturbed swallowing	4
Dyspnoea	2
Cosmetic complaints	9

Table 2 *Investigations performed on patients with a midline cyst*

Diagnostic procedures	*n*
Scintigraphy	14
Fistulograpy	7
CT scan	5
X-ray of the neck	6
Cytological puncture	3
Ultrasound	3

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Table 3 *Operative findings on patients with midline cysts*

	n	Cyst	Fistula	Combination	Hyoid *in situ*	Remnant of hyoid *in situ*	Hyoid removed previously
Primary operation	22	21		1	22	0	0
Recurrent	14		7	7	11	2*	1†

* Third and eleventh recurrence, respectively
† Fifth recurrence

months. In none of these patients was excision of the central part of the hyoid bone performed.

Discussion

The hyoid bone plays an important role in surgery of median cervical cysts. From post-mortem studies it appeared that the thyroglossal duct can pass directly anterior, posterior or even through the hyoid bone[2,3,5,9]. As early as 1893, not only the thyroglossal duct cysts were removed, but also the central part of the hyoid bone was excised because of this close relationship. This caused a fall in the recurrence rate from 50 per cent to 20 per cent[9]. Sistrunk additionally removed the more proximal duct-epithelium as far as the foramen caecum, with a core of lingual tissue. A further decrease in recurrence rate to 3 per cent was the result[8].

A cause for the development of recurrent cysts or fistulae is primarily the remaining duct epithelium in and around the remaining hyoid bone. In other cases, a branched thyroglossal duct can occur, so residual tracts can be left behind when only the main tract is removed. A third, not unimportant cause of recurrence, can be an existing infection, which obliterates the tract and anatomical landmarks. In these cases, total excision of duct-epithelium will become technically difficult[1,2,9]. Pollock and Stevenson[1] stated that 55 per cent of all patients with draining fistulae had a recurrence. According to Brown[11] and Ward[12] the recurrence rate increases after operations on infected tissues and at a younger age.

The importance of total excision, including the central part of the hyoid bone, also appeared from our group of patients. Thirteen of all patients who were operated on for recurrent cysts had their hyoid bone still in place. After operation, we found four recurrences out of fourteen patients in whom no excision of the hyoid bone was performed (29 per cent). No recurrences were found in 21 patients in whom the hyoid bone was excised. One patient developed a recurrent cyst despite the fact that the hyoid bone had already been removed in a previous operation. A deeper excision of tissue around the thyroglossal tract was performed, and no recurrence was seen. Ein *et al.*[9] also described three patients in their two hundred and seventy cases, who had recurrences after previous hyoid resection. These patients were all cured after deeper excisions.

Ectopic thyroid tissue is described in 1, 6–36, 5 per cent; carcinoma in epithelial remnants in < 1 per cent[3,4,6,7,10] Our figures are in accordance with these findings. In case of possible agenesis of the thyroid gland, some authors recommended a scintigram to prevent postoperative hypothyroidism. Because a median cervical cyst seldom gives diagnostic problems, other investigations are regarded as not relevant. The peroperative injection of the thyroglossal duct with methylene blue can help the surgeon determine the course of the tract.

From this study we conclude that for the prevention of recurrences after operative treatment of median cervical cysts, total excision of all thyroglossal duct epithelium, including the middle third of the hyoid bone, is necessary.

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Case reports

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Carcinoma of the ileostomy in a patient with familial adenomatous polyposis

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It is now well recognized that in familial adenomatous polyposis (FAP)[1] adenomas may be found in the stomach, duodenum and small intestine, in addition to the colon[2–4]. The malignant potential of these extracolonic adenomas is probably small, with the exception of periampullary lesions in the duodenum[5]. We describe a case of carcinoma of the ileostomy which occurred in metaplastic epithelium many years after proctocolectomy for FAP, and discuss the need for endoscopic surveillance of pelvic ileal reservoirs after conservative proctocolectomy.

Case report

A 72-year-old woman presented to the out-patient clinic complaining of swelling, irritation and bleeding from her ileostomy. She had undergone proctocolectomy for FAP in 1959

On inspection of the ileostomy, several small polyps were visible, and also an irregular mass of friable tissue which appeared to be invading the mucocutaneous junction. Preliminary biopsies suggested that the lesion was a villous adenoma: nevertheless, because of a strong clinicial suspicion of malignancy, a radical excision of the ileostomy together with the surrounding skin, subcutaneous fat, abdominal wall and distal ileum was performed A new ileostomy was fashioned in the left iliac fossa and the patient made a good recovery.

Pathological examination of the specimen confirmed the presence of a well-differentiated adenocarcinoma arising in a villous adenoma which had invaded into, but not through, the muscular wall of the ileum and did not involve local lymph nodes. The resection margins were free of tumour. Accompanying the adenocarcinoma were four small tubular adenomas, each of which was arising in an area of colonic metaplasia of the ileal epithelium, the normal ileal epithelium being free of tumours.

Review of the proctocolectomy specimen from 1959 confirmed the diagnosis of familial adenomatous polyposis, with no evidence of invasive adenocarcinoma or of adenomas in the short length of ileum resected

The patient remained well for the next 2 years, but at endoscopic examination of the stomach and duodenum was found to have multiple polyps in the stomach and duodenum. Biopsy of a duodenal polyp confirmed that it was a benign adenoma.

Discussion

Carcinoma of the ileum and carcinoma arising in an ileostomy are both rare[6,7]. However, adenomas arising in the small intestine of patients who suffer from familial adenomatous polyposis have been increasingly recognized in recent years. In general, the malignant potential of these adenomas is probably low but, as malignant change in the periampullary region of the duodenum is by no means rare, some authors[2] have advocated routine endoscopic surveillance of these patients. The frequency with which adenomas occur in the ileum in FAP is unknown, though Ohsato *et al.* report that six out of seven patients had polyps in the small bowel when they examined the intestine by means of the colonoscope at the time of colectomy[8]. Carcinoma developing in the ileostomy of a patient after colectomy for FAP has been reported only once previously[9]. It is interesting that the adenomas in our patient's ileostomy occurred in an area of colonic metaplasia. If colonic metaplasia predisposes to the formation of adenomas, then that would be relevant to more modern treatments of FAP such as conservative proctocolectomy. The incidence of polyposis in the ileal reservoir of such patients is not known, but the presence of polyps in a Kock type of ileal reservoir has been reported[10]. Wolfstein *et al.*[11] reported two patients with FAP in whom adenomatous polyps developed in the ileum after conservative proctocolectomy and ileo-anal anastomosis. However, the implications for FAP patients treated with ileal reservoir formation are perhaps more important. We know that the mucosa in an ileal reservoir usually undergoes colonic metaplasia[13] and if, as we believe, this mucosa is at risk of adenoma formation, then conservative proctocolectomy may not be a 'cancer free' alternative to colectomy and ileorectal anastomosis. Until further information is available we would suggest regular endoscopic surveillance of the ileal reservoir in FAP patients.

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Abnormal connecting duct between the common bile duct and the pancreatic duct

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The biliary and pancreatic duct system exhibits anatomical variations. Such variations may be a problem for the surgeon, but seldom harm the patient.

Endoscopic retrograde cholangic pancreaticography (ERCP) or percutaneous transhepatic cholangiography (PTC) provide the possibility of detailed radiographic visualization of the pancreatic and biliary duct system. Special anatomical variations may thus be discovered and several anatomical combinations have been documented[1-3]. An abnormally high union of the common bile duct and the main pancreatic duct is a well-known condition[4]. Usually it is combined with choledochal cyst[5] and a high risk of cancer in the bile ducts and gallbladder[6].

This paper describes a case of recurrent upper gastrointestinal meal-related pain due to the presence of an abnormal connecting duct between the common bile duct and the main pancreatic duct. Such an anatomical abnormality has not previously been described.

Case report

A 26-year-old woman with a 10-year history of recurrent meal-related pain localized in the right upper part of the abdomen was examined in May 1985. The pain attacks were accompanied by hyperamylasaemia up to 600 units/l (normal values 70–280 units/l). The pain was not accompanied by other symptoms. No history of alcohol or drug abuse was present. At ERCP the pancreatic duct was visualized and contrast medium was observed in the middle part of the common bile duct; a connecting duct between the common bile duct and the main pancreatic duct was demonstrated (*Figure 1*). The appearance was confirmed at a second ERCP.

Laparotomy was carried out in January 1986. The stomach, pancreas, extrahepatic biliary duct and intestines appeared macroscopically normal. The common hepatic duct, the cystic duct and the common bile duct were isolated. The abnormal connecting duct was found leaving the common bile duct as a side-branch 5 mm distal to the junction with the cystic duct. The connecting duct was ligated and divided but no histological examination was performed. The gallbladder was removed, and was found to be histologically normal. The patient was immediately relieved from her symptoms after the operation. One year later she is still doing well, with normal serum amylase and no pain.

Discussion

In a young woman, recurrent meal-related pain in the right upper quadrant of the abdomen was caused by the presence of an abnormal connecting duct between the common bile duct and the main pancreatic duct. Ligation and division of the connecting duct cured the patient completely. An explanation for the symptoms and the hyperamylasaemia in the present patient could be that the abnormal connecting duct allowed bile flux into the pancreas during meals causing pancreatitis and resultant hyperamylasaemia[7].

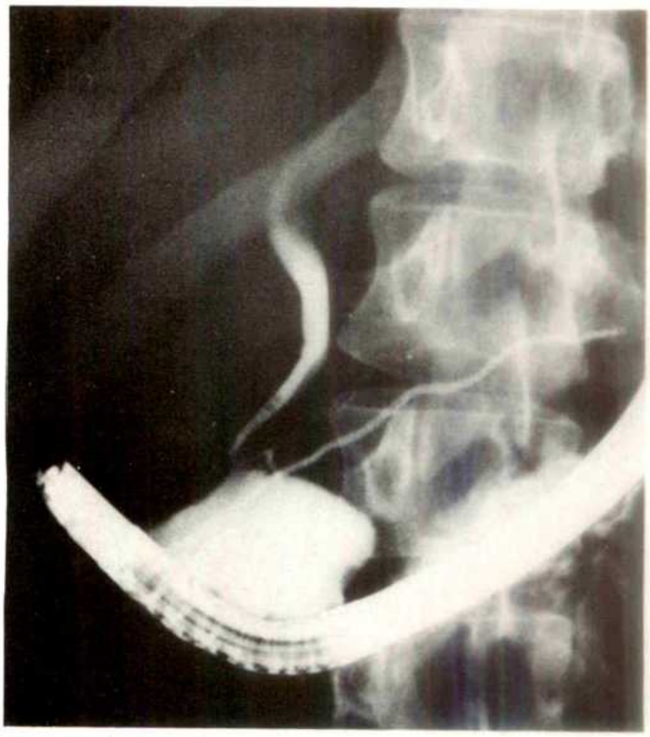

Figure 1 *Radiograph demonstrating the pancreatic duct and filling of the middle part of the biliary ducts over a connecting duct*

This report of a symptomatic abnormal connecting duct between the common bile duct and the main pancreatic duct underlines the importance of ERCP as an examination for patients with inexplicable upper gastrointestinal symptoms and hyperamylasaemia.

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Traumatic disruption of the gallbladder evaluated by computerized tomography and magnetic resonance imaging

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Isolated gallbladder perforation from blunt trauma is uncommon. The usual clinical course is one of slowly worsening vague abdominal manifestations. The difficulty in diagnosis is the reason that the time from injury to laparotomy is typically over 1 week[1-3]. Less frequently, traumatic gallbladder perforation presents as an acute abdomen[4]. The diagnosis can be suspected sonographically[5,6] or radiologically with transhepatic cholangiography, HIDA, liver–spleen scan, or computerized tomography[2,5,6]. We report here a case of traumatic gallbladder perforation and biliary ascites evaluated by computerized tomography (CT) and magnetic resonance imaging (MRI).

Case report

A 36-year-old white man was assaulted on the evening before presentation with blows to the abdomen. He complained of pain in the right lateral lower rib region. He was minimally tender here and had good bowel sounds. His pulse was 105/min with a blood pressure of 110/92 mmHg and no orthostatic changes. Initial laboratory studies showed a haemoglobin of 16·3 g/dl, amylase 213 units/dl, and normal electrolytes. Plain films showed no fractures but there was a small right pleural effusion. His haematocrit remained stable. Liver function tests included an alkaline phosphatase of 141 units/l, bilirubin of 1·8 mg/dl, lactate dehydrogenase 941 units/l and glutamic oxaloacetic transaminase 228 units/l. Because of the paucity of the patient's symptoms, peritoneal lavage and non-invasive imaging were not performed at this early stage.

Over the next few days, the patient had persistent mild diffuse abdominal symptoms with nausea, gas and low-grade fevers. A CT scan of the abdomen and pelvis was obtained with intravenous contrast 7 days after injury (*Figure 1*). This showed a free fluid collection within the abdomen and pelvis. A haematoma was seen in the medial segment of the left hepatic lobe.

MRI (*Figure 2*) was performed the same day using a Picker MR scanner with a field strength of 0·5 T. T1- and T2-weighted axial images were obtained*. The fluid collection was of decreased signal intensity (dark) on T1-weighted images and increased signal intensity (bright) on T2-weighted images. Whereas this would not be unusual for acute haemorrhage (less than 48 h) or non-haemorrhagic fluid collections, if this represented haemorrhage of 7 days' duration the T1- as well as T2-weighted images should appear bright[7,8]. The abnormality seen in the medial segment of the left hepatic lobe on CT was isointense with normal hepatic parenchyma on T1 images and focally hyperintense on T2 images. The gallbladder was flaccid.

Based on these findings, the suggestion was made that the patient had a contained liver laceration with concomitant non-haemorrhagic ascites from other causes, possibly from a biliary rupture and bile leak. The patient's abdomen was tapped with production of grossly bilious fluid. Exploratory laparotomy revealed a 1-cm perforation of the posterior body of the gallbladder near the liver with bile staining of the entire peritoneal cavity. There was a haematoma in the medial segment of the left lobe of the liver. A cholecystectomy was performed and intra-operative cholangiography showed free flow into the duodenum without extravasation. The abdomen was irrigated and drains placed. Postoperatively, the patient did well and was discharged soon thereafter.

Discussion

This case typifies the difficulties in evaluating traumatic gallbladder disruption. As in most previous reports, the time from injury until surgical intervention was delayed with persistence of vague, non-specific abdominal findings.

In this case we were uniquely able to compare CT and MRI in assessing biliary ascites. Where CT is sensitive for identifying fluid collections, it is poor in discriminating types of fluid. Recent advances in MRI often make it possible to identify the nature of a fluid collection[7-9]. In haemorrhage less than 48 h old, blood is indistinguishable from ascites, appearing dark on T1-weighted images and bright on T2-weighted images[7,8]. In its subacute phase (2 days to months), the blood is hyperintense on both T1- and T2-weighted images[7,8]. This is thought to result from conversion of haemoglobin to methaemoglobin which shortens the T1 relaxation time of tissues and emits a stronger signal on T1-weighted images[8]. The lack of signal on T1-weighted images in a case of suspected subacute abdominal haemorrhage suggests that the process is non-haemorrhagic and may involve leakage of bile, urine, or pancreatic fluid[9]. Chronic haemorrhage (months to years) can appear dark on both T1- and T2-weighted images because of the paramagnetic effects of haemosiderin and calcium[7,10].

Both CT and MRI correctly identified the liver haematoma in our patient. However, MRI correctly identified the fluid collection as non-bloody, which was a unique advantage over CT. MRI is non-invasive and accurate and will certainly be important in evaluating many types of surgical abdomens, as demonstrated in this relatively rare case of traumatic gallbladder disruption.

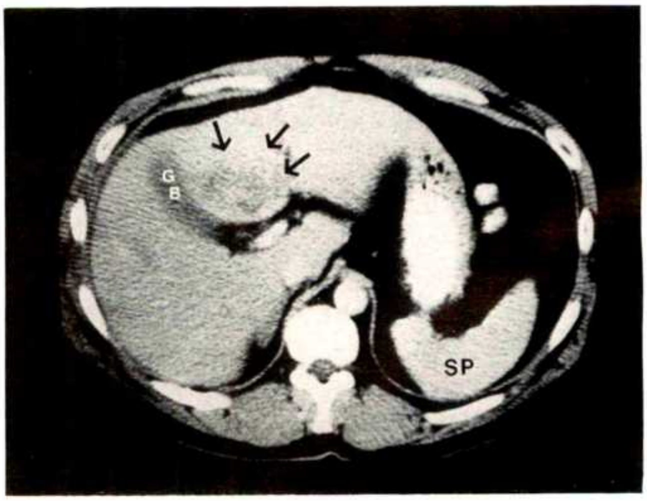

Figure 1 *CT scan of upper abdomen with intravenous contrast. The section which is at the level of the gallbladder (GB) shows a hypodense lesion (arrows) in the medial segment of the left lobe of the liver*

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* *T1-parameters: TE (time to echo), 26 ms; TR (repetition time), 683 ms. T2 parameters: TE, 100 ms; TR, 2100 ms with motion artefact suppression*

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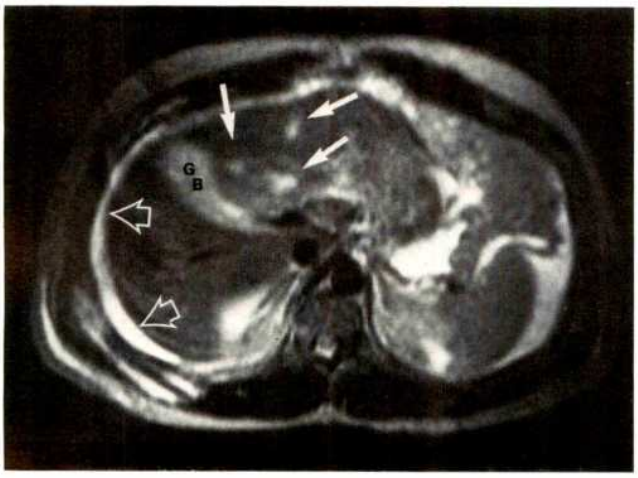

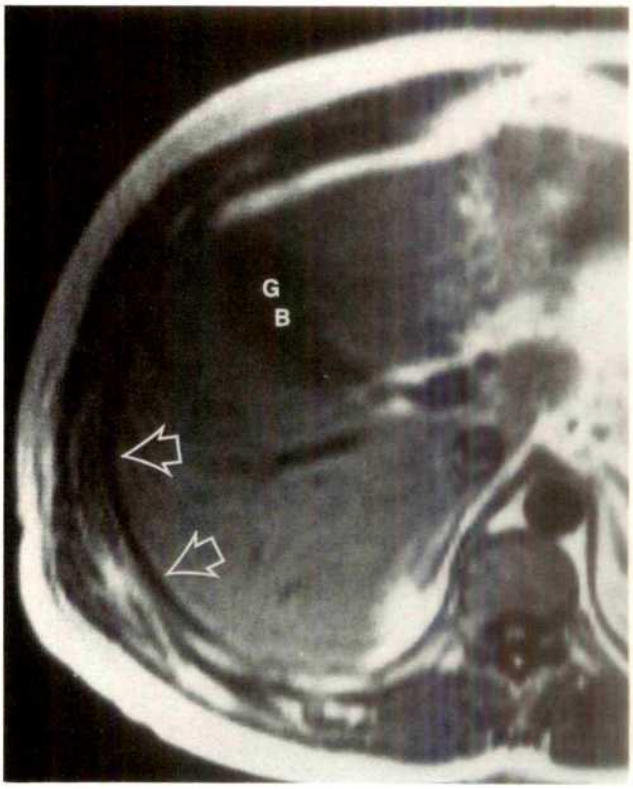

Figure 2 *MRI scan of the upper abdomen. Left, T2-weighted sequence through the level of the gallbladder (GB) demonstrating small foci of hyperintensity (arrows) within the area of CT abnormality in the medial segment of the left hepatic lobe. The intraperitoneal fluid (open arrows) around the right liver margin is hyperintense. Right, T1-weighted sequence, right abdomen, at the level of the gallbladder (GB). The lesion in the medial segment of the left lobe of the liver is nearly isointense with liver parenchyma. The intraperitoneal fluid along the right liver edge is of markedly decreased intensity (open arrows)*

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The Vascular Surgical Society of Great Britain and Ireland

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The following abstracts are from a selection of the papers presented at a meeting of The Vascular Surgical Society of Great Britain and Ireland, held at The Civic Centre, Newcastle upon Tyne on 26 and 27 November 1987. (President: Mr P. H. Dickinson.)

Can the outcome of femorodistal bypass be predicted?

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An adequate blood flow is known to be important for the continued patency of femorodistal bypass grafts. In the past, flow measurements have been largely confined to electromagnetic flowmeters which are expensive and often difficult to use.

Using a Doppler flowmeter various haemodynamic parameters were measured during 47 femorodistal *in situ* vein grafts to determine the best predictor of early graft function. Measurements included the proximal (inflow) resistance, the graft blood flow, the proportions of blood flowing distally and retrogradely at the distal anastomosis and the peripheral (outflow) resistance before and after papaverine. Success at 1 month was defined as a patent graft with increased ankle pressures and a clinical improvement (35 out of 47).

No one parameter completely distinguished between success and failure but discriminant analysis of all parameters predicted success with a sensitivity of 100 per cent and a specificity of 92 per cent. A simpler combination of a peripheral resistance after papaverine <1 Peripheral Resistance Unit and a retrograde blood flow of <33 per cent predicted success with a sensitivity of 97 per cent and a specificity of 83 per cent.

These criteria have been used to predict success in a further 26 consecutive femorodistal grafts with a sensitivity of 88 per cent and a specificity of 75 per cent. Ten technical errors were also detected and successfully corrected.

The Doppler flowmeter is inexpensive and easy to use compared with electromagnetic devices. Its use during femorodistal bypass enables technical errors to be located and graft function to be accurately predicted.

Lessons learned from 334 consecutive in situ bypass grafts

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Since October 1983 we have implanted 334 *in situ* saphenous vein bypass grafts in an elderly population (median age 72 years) of 187 men (56 per cent) and 147 women (44 per cent). These patients had a history of diabetes (42 per cent), hypertension (48 per cent), heart disease (41 per cent) and smoking (68 per cent). The operations were performed for limb salvage (gangrene 34, rest pain 23 and ulcer 13 per cent), claudication (27 per cent) or aneurysm (4 per cent). There were 304 single-segment, 25 composite, 3 sequential and 2 interposition grafts. Grafts originated at the common (47 per cent), deep (17 per cent), superficial (24 per cent), popliteal (6 per cent), tibial (1) and iliac (1) arteries and aortofemoral Dacron grafts (5 per cent); they terminated at the suprageniculate (6 per cent) or infrageniculate (50 per cent) popliteal artery or infrapopliteal artery (44 per cent); 15 per cent were extended to the ankle or foot. The 1-month mortality rate was 2·9 per cent and the 3-year survival rate was 65 per cent. Primary patency rates were 91 (1 month), 85 (1 year) and 77 per cent (3 years); secondary patency was 96 (1 month), 91 (1 year) and 84 per cent (3 years). The superficial and deep femoral and the popliteal arteries, having 1-year patency rates of 95, 91 and 86 per cent respectively, were as effective as the common femoral (91 per cent, 1 year patency) as inflow sites. A significant rate of failure was noted in the second postoperative year in patients operated on for gangrene: the 2-year patency rate (67 per cent) was lower than that of the claudication (96 per cent), ulcer (91 per cent) and rest pain (86 per cent) groups. Diabetes did not appear to affect graft failure. Infrageniculate grafts (popliteal 85, infrapopliteal 81 per cent) had similar 3-year patency rates. Bypasses to the ankle and foot were also successful with 1- and 2-year patency rates of 94 and 84 per cent. Suprageniculate bypasses had unexpectedly low patency rates; 1 month (84 per cent), 1 year (78 per cent) and 2 years (66 per cent). Based on this experience the *in situ* technique has become our preferred method for femorodistal revascularization. The *in situ* bypass is increasingly advantageous for more distal anastomotic sites and longer grafts.

Surgical optimism in critical lower limb ischaemia

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Chronic critical ischaemia of the lower limb[1] is an inexorable process that can only be halted by death, amputation or vascular reconstruction. Prognosis after amputation in these patients is poor but can reconstruction be justified? Since January 1985 our policy has been to attempt revascularization whenever technically possible. Using a minimum follow-up of 6 months, 158 patients (165 limbs) fulfilled the criteria for critical ischaemia. In all, 12 were treated by primary amputation and reconstruction was attempted in the remaining 153 (92·7 per cent).

Inflow procedures were required in 44 limbs (28 with distal reconstruction). In total, distal bypass was performed in 137 limbs extending to calf vessels in 105. Long saphenous vein was utilized when possible but transposed vein had to be used on 29 occasions and prosthetic material on 4.

A total of 114 (74·5 per cent) limbs were successfully revascularized. Thirty-five patients have died with a functioning graft, sixteen within 1 month of operation. In all, 94 per cent of the survivors can walk unassisted. The graft failed in 39 cases (17 within 1 month): 29 thrombosed, 7 were ligated after haemorrhage and 3 failed to reverse the ischaemia despite remaining patent. This resulted in 8 deaths, 22 amputations and 9 survivors with persisting ischaemia.

Reconstruction can be offered to a surprisingly high proportion of patients with critical lower limb ischaemia with acceptable mortality and good prospects for rehabilitation.

1. Bell PRF, Charlesworth D, DePalma RG *et al. Br J Surg* 1982; **69** (Suppl) S2.

Indications of graft failure in femoropopliteal bypass

G. Kenchington, R. Dain, N. Weston and C. Marshall for the Femoro-Popliteal Trial participants.

The MRC funded multicentre femoropopliteal bypass trial on antiplatelet drugs and prosthetic materials provides a unique opportunity to investigate risk factors that influence subsequent patency.

Of 550 patients recruited, follow-up was sufficient for entry on computer in 425. Clinical, operative, Doppler, haematological and biochemical records were maintained by study co-ordinators, who also determined graft patency objectively. Life tables were plotted for each risk factor and compared by χ^2 test.

In saphenous vein bypass ($n=293$) cumulative patency ($\pm$s.e.m.) at 12 and 24 months was $77 \pm 0{\cdot}03$ and $76 \pm 0{\cdot}03$ per cent respectively. Of the 67 failed grafts, 48 occluded within 6 months and only 3 after 12 months. Vein patency was not influenced by reversed or *in situ* technique, anastomosis above or below knee, serum cholesterol, haemoglobin, platelet count, graft length or indications for surgery. Patency was significantly impaired by smoking history, serum triglycerides, and poor quality vein reported at operation ($P<0{\cdot}05$). Proximal anastomosis to the superficial or profunda femoris or distal anastomosis to the tibioperoneal trunk tended to improve patency ($P<0{\cdot}1$, $P<0{\cdot}05$). In contrast, prosthetic graft ($n=132$) patency fell to $67 \pm 0{\cdot}04$ per cent by 2 years ($P<0{\cdot}001$), was not influenced by triglycerides or smoking, but was impaired by surgery for rest pain and below knee anastomosis, particularly to the tibioperoneal trunk ($P<0{\cdot}05$). Disease at the distal anastomosis and short template bleeding time were associated with failure in both vein and prostheses.

Multivariate analysis of these prognostic indicators should allow pre-operative assessment of prognosis in femoropopliteal bypass, but saphenous vein and prosthetic risk must be calculated separately.

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Strictures in femoropopliteal vein grafts

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A total of 80 patients drawn from a randomized trial of *in situ* and reversed vein grafts for femoropopliteal bypass had their grafts surveyed by intravenous digital subtraction angiography (IV DSA) 3–6 months after operation. All patients were asymptomatic with clinically patent grafts at the time of examination. Fibrous strictures were identified in a total of 24 grafts (30 per cent). There were strictures in 14 out of 39 (36 per cent) reversed grafts and in 10 out of 41 (24 per cent) *in situ* grafts ($\chi^2=1·93$ n.s.). The strictures were characterized for site, length and severity of stenosis. Follow-up of the patients showed that 5 of the 24 grafts with strictures (21 per cent) occluded within 2 years after the DSA examination compared with 4 occlusions out of 56 grafts (7 per cent) where there was no evidence of stricture ($\chi^2=4·67$, $P<0·05$). Further survey of the remaining patent grafts by IV DSA is being undertaken to assess any change in established strictures or new stricture formation

The results to date indicate that fibrous stricture formation in vein grafts is associated with a three-fold risk of subsequent graft occlusion. All vein grafts should therefore be monitored for the development of strictures with a view to prophylactic therapy The optimum method of treatment remains to be determined

Should non-haemodynamically significant vein graft stenoses be repaired?

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Eighty femorodistal *in situ* vein bypass grafts with normal operative arteriograms were evaluated postoperatively at 3-monthly intervals with clinical assessment, ankle:brachial pressure indices (ABI), intravenous digital subtraction angiography (IV DSA) and Duplex scanning. Graft stenoses were identified by IV DSA and/or by Duplex scan. They were classified as haemodynamically significant on the basis of: the development of symptoms, and/or a decline in ABI > 0·2

Five grafts (6 per cent) occluded in the perioperative period. Of 75 grafts 68 (91 per cent) remained patent at a mean follow-up time of 8 months (range 3–12 months). However, stenoses have been identified in 19 grafts (25 per cent). All were detected by Duplex using peak systolic velocity criteria. Duplex derived flow measurements were found to be inaccurate and non-reproducible. All stenoses have been confirmed by angiography although two were initially 'missed' by IV DSA Five graft stenoses became haemodynamically significant during follow-up and were successfully repaired. However, three of the fourteen grafts with non-haemodynamically significant stenoses occluded without developing warning symptoms or a decline in ABI.

The data reveal a high incidence (i.e. 25 per cent) of femorodistal vein graft stenoses developing within the first postoperative year These are accurately and non-invasively detected by duplex scanning Only 11 of 19 non-haemodynamically significant graft stenoses (58 per cent) remained asymptomatic. Within 6 months of detection, five had developed symptoms and were successfully repaired but three occluded without warning and could not be salvaged.

Thoraco-abdominal aneurysms

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Thoraco-abdominal aneurysms are uncommon and pose special problems in management. We report a consecutive series of 23 such aneurysms managed over a 5-year period

Nineteen patients presented with epigastric/back pain, one with dysphagia, one as a collapse and in two the aneurysm was a chance finding. Male patients predominated (19 male, 4 female) the median age being 68 years

CT scanning accurately assessed the extent of the aneurysms in all 13 patients scanned, ultrasound and physical examination were of little value.

Risk factors predicting a morbid outcome were ischaemic heart disease, hypertension, transient ischaemia attack or stroke, lung disease and renal failure. A thoraco-abdominal approach was used in all patients. The mean peroperative blood loss was 5·5 litres (range 2000–12 000 ml). Hypotension on declamping visceral and/or limb vessels occurred in 12 patients all of whom died A consumptive coagulopathy was observed in eight patients in the first half of the series. Five patients are alive and well, eighteen died. At post mortem the causes of death were myocardial ischaemia (ten), renal failure (five), ischaemic colitis (one), bronchopneumonia (one) and perforated duodenal ulcer in one Paraplegia occurred in three, all of whom died. We recommend that careful consideration be given to the aforementioned risk factors, per- and postoperative hypotension are avoided and that platelets and fresh frozen plasma be used in conjunction with whole blood to avoid coagulopathies.

Haemodynamic consequences of femorofemoral bypass grafts

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Although femorofemoral (FF) grafting was originally used as a method of limb salvage, it is now increasingly being used in patients with claudication. If this trend is to be supported then the haemodynamic consequences of the operation must be carefully assessed. A review of 42 FF grafts revealed 3 patients who had developed postoperative donor limb claudication Subsequently, we have performed intra-operative haemodynamic assessment of 15 patients undergoing FF grafting The brachial and femoral arterial pressures were recorded after cannulation and the femoral arterial flow rate was measured using a Doppler flowmeter. The inflow resistance was calculated from these values and expressed as peripheral resistance units (1 PRU = 1 mmHg $\text{ml}^{-1}\,\text{min}^{-1}$) The ankle brachial pressure indices (ABPI) of donor limbs were measured pre- and postoperatively.

	Number of patients	Decrease in APBI > 15%	Donor limb symptoms	Inflow resistance (PRU)
Group A	8	–	–	≤0·05
Group B	5	+	–	>0·05<0·10
Group C	2	+	+	≥0·10

The results demonstrate that the measurement of inflow resistance at operation accurately identifies the potential for subclinical and clinical steals to develop One patient in group A had an initial inflow resistance of 0·13 PRU but after peroperative Gruntzig balloon dilatation of the donor iliac artery this fell to 0·02, thus preventing a third clinical steal

The primary requirement for FF grafting is unimpeded flow through the donor iliac segment which requires careful assessment. We strongly recommend haemodynamic studies especially as the availability of balloon angioplasty makes inflow iliac disease amenable to treatment.

Blood flow measurement in the diabetic foot as an indication of arteriovenous shunting

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A total of 120 diabetic patients without occlusive vascular disease have been studied. They were divided into three equal groups based on the results obtained using biothesiometry: group 1, diabetics with neither neuropathy nor ulceration (D); group 2, diabetics with neuropathy but without ulceration (DN), and group 3, diabetics with neuropathy and associated ulceration (DNU)

Forty controls were also studied who had neither diabetes nor vascular disease. The patients and controls were all studied using continuous wave ultrasound, photoplethysmography (PPG), laser Doppler flowmetry (LDF), and transcutaneous oxygen measurements (P_{tc,O_2})

Spectral analysis was performed on the ultrasonic pedal waveform A pulsatility index (PI) < 7·6 was considered indicative of decreased peripheral resistance. A venous refilling time of ≤ 18 s as measured by PPG was classified as abnormally rapid. LDF was used to assess skin blood flow over the dorsum of the foot both in the supine and dependent position. The ratio of dependent to supine flow was calculated P_{tc,O_2} was also measured over the dorsum of the foot whilst inhaling 35 per cent oxygen. Recordings were obtained again both in the supine and dependent position and a ratio developed.

The percentage of abnormal results for each of the three groups of diabetics which fall outside the fifth centile range when compared with controls are shown in the *Table.*

	D	DN	DNU
PI	27·5	45	95
PPG	20	27·5	67·5
LDF	7·5	27·5	40
P_{tc,O_2}	15	25	45

All values are percentages

The results demonstrate a measurable alteration in the characteristic of skin blood flow associated with deteriorating clinical status and appear to be indicative of progressive arteriovenous shunting.

Autologous transfusion of selective blood components in aortic surgery

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Autologous blood transfusion avoids the risk of hepatitis or HIV but coagulation factors may still require replacement in aortic surgery. Pre-operative selective haemodilution may prevent pulmonary micro-embolization following release of aortic clamps while preserving red cells, platelets and clotting components for re-infusion

Before standardized aortic surgery involving 1·5 h cross-clamping and 1 h hypotension, 16 pigs were randomized to either selective haemodilution reducing platelets and clotting factors by 60 per cent and haematocrit by 30 per cent (Haemonetics V-50 cell separator) or control. Platelet and leucocyte counts, cardiac output, pulmonary vascular resistance (PVR), arterial P_{O_2}, alveolar-arterial P_{O_2} difference (A_{ad,O_2}) and pulmonary shunt were measured pre-operatively, on aortic clamp removal and at 3 days, using arterial and Swann–Ganz catheters.

In haemodiluted pigs, platelet and leucocyte counts (mean ± s.e.m.) were reduced pre-operatively from 441 ± 50 to 113 ± 9 × 10^9/l and from 20·4 ± 1·1 to 12·6 ± 0·8 × 10^9/l respectively ($P<0\cdot001$), but were restored after surgery to 331 ± 59 × 10^9/l and 17·0 ± 1·8 × 10^9/l by autologous retransfusion. Despite similar cardiac outputs the PVR after aortic declamping of 1286 ± 112 dynes s^{-1} cm^{-5} m^{-2} in controls was reduced to 1011 ± 79 by cell separation with a consequent improvement in P_{a,O_2} from 88 ± 5·5 to 103 ± 5·0 mmHg ($P<0\cdot05$). On the third postoperative day pulmonary shunting in haemodiluted pigs was only 4·4 ± 1·2 per cent compared with 8·8 ± 2·8 per cent in controls, with A_{ad,O_2} consequently improved at 13·4 ± 4·7 mmHg compared with 20·7 ± 4·5, but as three control and one haemodilution animals died these differences failed to achieve significance

Selective haemodilution by cell separation reduces the pulmonary consequences of releasing aortic crossclamps, while subsequent autologous retransfusion preserves fresh platelets, leucocytes and clotting factors.

Micro-particulate debris in Solcotrans autotransfusion

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The Solcotrans autotransfusion system employs no cell-washing facility, relying on filtration for removal of salvaged particulate debris In 17 patients undergoing elective aortic surgery, we have measured the amount of microparticulate debris (MD) in the Solcotrans reservoir (29 devices), and after filtration under pressure with either: Pall Ultipor 40 μm screen filter (10 patients, 16 filters); or GB Microsept 60/20 μm screen filter (7 patients, 13 filters) Using a Coulter ZM and Channelyser 256, the size–frequency distribution of MD per ml salvaged whole blood was recorded for three MD diameter ranges. Screen filtration pressure (SFP in mmHg) measurement was simultaneously performed. Bank whole blood is quoted for comparison Initial morphological examination of these MD by transmission electron microscopy demonstrates fibrin strands, platelet clumps and cellular fragments.

Table *The uncorrected mean number of microparticulate debris per ml of blood*

	<20 μm	20–40 μm	>40 μm	SFP
Reservoir	5537 ± 4313	8378 ± 5572	1430 ± 1010	>450
Post-Ultipor	4528 ± 2592	5495 ± 3608	404 ± 361	287 ± 212
Post-Microsept	3145 ± 3108	2513 ± 3085	35 ± 27	37 ± 18
Bank 21–35 days	5997 ± 3215	11745 ± 5040	2048 ± 1325	

The results are mean ± s d.

In conclusion, the Solcotrans reservoir contains no more MD than 21–35-day-old citrate-phosphate-dextrose A1 bank blood. Routine use of the GB Microsept 60/20 filter during Solcotrans re-infusion will significantly reduce the size and numbers of such re-infused particles when compared with the Pall filter. The clinical effect of re-infusion of such salvaged MD requires further investigation.

Endothelial seeding of ePTFE vascular grafts: a clinical trial

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Animal studies have suggested that patency rates of prosthetic vascular grafts may be improved by 'seeding' autologous endothelial cells into the graft lumen at the time of graft implantation Clinical experience of this procedure is sparse.

We have performed a randomized controlled clinical trial using a technique whereby endothelial cells were harvested mechanically from long saphenous vein and introduced into ePTFE small calibre grafts (mainly infra-inguinal) The objective was to establish whether this resulted in improved patency rates, and whether this was directly related to endothelization of the graft.

A total of 50 patients were randomized to receive seeded (22) or non-seeded (28) grafts. Follow-up was by regular clinical examination complemented by digital subtraction angiography at 7 days, 3 and 12 months postoperatively. Indium-111-oxine labelled platelet scans were performed at 7 days and 3 months.

Follow-up at 14 months has shown an early trend towards improved patency in the seeded group This is not maintained, however, the reverse occurring at 8 months. The differences in patency were not statistically significant at any time. Platelet scans did not reveal any convincing evidence of endothelialization. However, histology in one of four seeded grafts explored for thrombosis revealed the presence of endothelium around 50 per cent of the graft circumference.

On the evidence of this trial, we conclude that endothelial seeding of ePTFE grafts using mechanical harvesting has not resulted in a fully endothelialized graft or improved patency rates. Further studies, using an enzymatic harvesting method, are indicated

Role of Duplex scanning pressure indices and the penile/brachial index in impotence evaluation

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The penile/brachial index (PBI) is widely used as a non-invasive screening test for vasculogenic impotence. Doubts have been raised regarding its reliability. Duplex scanning has recently been advocated as a more accurate investigation.

A total of 26 impotent patients have been investigated using a Diasonics DRF 400 scanner. Deep and dorsal artery diameters and velocities were measured before and after 60 mg of intracorporeal papaverine. Patients were grouped according to erectile response Results were compared with the pressure indices at both ankles, and the PBI was measured with an 8 MH$_z$ pencil probe

The results showed that the erectile response correlated well with the increase in deep artery flow ($r=0\cdot84$, $P<0\cdot001$) and increase in deep artery diameters ($r=0\cdot6$, $P<0\cdot001$). The penile/brachial index and dorsal artery response correlated less well ($r=0\cdot5$, $P<0\cdot005$ and $r=0\cdot4$) Only in those patients with a good erectile response were bilateral deep artery peak velocities >25 cm/s found. There was poor correlation between the erection obtained and the pressure indices. Deep artery flow following injection correlated poorly with the penile/brachial index ($r=0\cdot4$) and although nine of ten patients with a good erection had a

PBI >0·7, it should be noted that 9 of the remaining sub-optimal responders (16) also had this finding.

In conclusion, the PBI is a poor measure of vasculogenic impotence because it probably relies on the pressure in the superficial arteries. Duplex scanning would seem to be the investigation of choice as both superficial and deep arteries can be identified with certainty.

Saphenous ligation for venous ulcer in presence of co-existent primary deep incompetence

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Clinical and Doppler examination were combined with ascending and descending venography to define the morphology of the venous system in 100 limbs with ulceration. Various combinations of abnormalities were identified.

Abnormalities	No. of limbs
Perforator incompetence alone	6
Perforator/saphenous incompetence	29
Perforator saphenous deep incompetence	31
Perforator deep incompetence	11
Post-phlebitic change ± other	23
Total number of limbs studied	100

By these means a group of patients can be identified with perforator and primary saphenous and deep incompetence (*Table*).

This study examines the impact of saphenous ligation and excision in this, the largest single group of 31. In nine out of ten patients undergoing surgery for the first time, the ulcer remains healed after a minimum follow-up of 3 years. Photoplethysmography and dorsal foot vein pressures measured postoperatively in six such limbs with grade III/IV femoral incompetence remained significantly abnormal compared with control limbs. Within this group of 31 limbs were 9 with recurrent saphenofemoral incompetence. Eight have undergone religation of this incompetence; in 6 there has been no clinical improvement at follow-up.

Preclinical changes of lipodermatosclerosis in 'normal' limbs

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In a recent study[1], we found low transcutaneous oxygen levels in the clinically normal skin of the contralateral limbs in patients with unilateral venous ulceration, suggesting that a diffusion block precedes the visible skin changes. This may be the result of pericapillary fibrin deposits.

A total of 17 patients with unilateral venous ulceration had skin biopsies from the gaiter area and thigh of the contralateral limb. This skin was examined by immunofluorescence for fibrin and laminin. Transcutaneous oxygen measurements, foot volumetry and ascending phlebography were also performed

Of the 17 limbs 14 had evidence of pericapillary fibrin deposits in the dermis of the gaiter skin. This was scored as a ratio of the number of capillaries staining for fibrin and the total number staining for laminin. There was a statistically significant correlation between the fibrin score and the transcutaneous oxygen ratio (correlation coefficient 0·578, $P = 0·014$). There was no significant correlation between the fibrin score and the half volume refilling time (a measure of venous reflux), the relative expelled volume (a measure of the pumping function of the calf muscle), euglobulin clot lysis time (an index of fibrinolytic capacity), or plasma fibrinogen levels There was no significant difference between the fibrin scores for limbs with and without post-thrombotic changes on ascending phlebography.

In 82 per cent of these 'at risk' limbs that have been sampled, perivascular fibrin has already appeared before the development of any clinical skin changes, and the presence of this fibrin has been shown to correlate with the skin's capacity for oxygen diffusion Treatment at this stage may help to prevent the future development of venous ulceration.

1. Stacey MC, Burnard KG, Pattison M, Lea Thomas M, Layer GT. Changes in the apparently normal limb in unilateral venous ulceration. *Br J Surg* 1987; 74: 936–9.

Aetiology influences late morbidity following axillary–subclavian vein thrombosis

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Contrary to initial clinical impressions, upper limb venous thrombosis is now recognized as a cause of significant long-term morbidity. This study aims to relate the frequency and severity of late morbidity to aetiology in axillary–subclavian vein (ASV) thrombosis.

Twenty-two patients presenting with ASV thrombosis have been reviewed. Follow-up data were available from 3 to 72 months (median 18 months). Patients were treated conservatively with anticoagulants alone (15) or by thrombolysis followed by anticoagulation (2). Three patients presenting with symptoms of more than 3 months duration and two asymptomatic patients were not anticoagulated. Oral anticoagulation was continued for periods ranging from 6 weeks to 5 months (median 3 months). Patients were classified into four groups based on aetiology: group 1, external trauma and effort related, group 2, stasis/hypercoagulability; group 3, central venous catheterization; and group 4, no cause identified. Two non-fatal pulmonary emboli occurred, one each in groups 1 and 2. Late symptoms were scored (0–3) as follows· asymptomatic (0), mild symptoms on sustained activity (1), mild symptoms on normal activity (2) and severe, disabling symptoms on normal activity (3). A late morbidity index has been calculated for each group as the percentage of the maximum possible score for that group Results are shown below:

	Group 1	Group 2	Group 3	Group 4
No. of patients	4	6	6	6
No. symptomatic	2 (50)	3 (50)	1 (17)	1 (17)
Morbidity index (%)	41·7	33·3	5·6	16·7

Values in parentheses are percentages

These results suggest that aetiology plays an important role in determining the outcome of ASV thrombosis. This finding may be of significance in selecting patients for aggressive treatment options.

Radiological follow-up of caval interruption procedures

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Four groups of patients have been reviewed using Duplex ultrasound and conventional radiographic techniques. They include: 2 out of 14 after caval plication; 10 out of 32 after Mobin–Uddin filter; 5 out of 5 after Kimray–Greenfield filter and 12 out of 16 after Gunther filter insertion. The mean duration of follow-up was 9·5, 8·6, 3·7 years and 4·7 months, respectively.

Duplex satisfactorily examined 27 out of 29 patients, unsatisfactory examinations in 2 patients were attributed to obesity.

Of the two patients who had caval plication procedures, one had complete caval occlusion. Of the ten Mobin–Uddin filter patients, two had unsatisfactory ultrasound examination while eight were shown to have occlusion of the inferior vena cava. Of the 5 Greenfield filter patients four had normal caval flow while one showed narrowing of lower inferior vena cava. Of the 12 Gunther, 11 had normal caval flow and calibre while 1 showed caval occlusion.

Two out of ten Mobin–Uddin filters were low in position or showed angulation. One out of five Greenfield filters was low; eight out of twelve Gunther filters showed downwards migration, four of these showing breakage of one or two of the twelve anchoring wires.

Short-term follow-up suggests that the new Gunther filter has a similar satisfactory caval patency rate to the Greenfield filter. The Mobin–Uddin filter caval patency rate is low as is that associated with operative interruption.

The Gunther filter has the advantage of easy percutaneous placement through a 10F sheath as opposed to venotomy required for insertion of the 24F Greenfield sheath. All three filters reviewed have a tendency to migrate downwards. The associated wire breakage in the Gunther filters is a disappointing defect in an otherwise attractive device.

Platelet deposition following carotid endarterectomy relates to subsequent intimal thickening

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Platelet deposition following endarterectomy, with release of growth factors, may promote intimal hyperplasia. We studied the relationship between radiolabelled platelet deposition in patients immediately after carotid endarterectomy and subsequent luminal narrowing.

Progressive autologous ^{111}In-platelet accumulation was measured from the second postoperative day for 3 days in 40 patients after unilateral carotid endarterectomy. Daily increases in the ratio of radioactivity over the operated and contralateral artery were expressed as thrombogenicity index (TI). Luminal narrowing, measured 1 year later by peak frequency on continuous-wave ultrasound and biplanar Duplex imaging, was calculated as the percentage reduction in cross-sectional area.

Patients with TI above the median of 0·18 subsequently developed mean (±s.e.m.) luminal narrowing of $32·5 \pm 5·6$ compared with $15·0 \pm 4·1$ per cent when postoperative thrombogenicity had been in the lower half of the range ($P < 0·03$). There was a direct correlation between this early postoperative platelet accumulation and subsequent narrowing at 1 year ($r = 0·39$, $P < 0·02$). Excluding the ten patients who had patches, with widened lumens and higher initial TI of $0·28 \pm 0·02$, this correlation improved to $r = 0·45$ ($P < 0·02$).

Luminal narrowing of the carotid, which may reflect intimal thickening due to hyperplasia, was related to platelet deposition at the endarterectomy site immediately after surgery

Internal carotid artery bypass: a new surgical approach to carotid artery stenosis

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Although considerable debate surrounds the indications for surgery to the internal carotid artery, surprisingly little attention has been given to the inherent inadequacies of endarterectomy, the procedure presently used in most centres Reported postendarterectomy restenosis and occlusion rates vary from 1 to 49 per cent, our own experience showed an 18 per cent occlusion rate Surprisingly few centres report careful follow-up studies after carotid artery reconstruction. Further, endarterectomy at other sites has been generally abandoned in favour of autogenous vein or prosthetic bypass grafts.

We now report our experience with 37 consecutive cases of symptomatic carotid artery disease treated by autogenous vein bypass. After harvest of the saphenous vein and identification of the full extent of the carotid disease, the bypass is performed with the vein reversed and mounted on an indwelling shunt

Postoperative follow-up is performed at 3-monthly intervals using clinical assessment and Doppler ultrasound and at 6-monthly intervals using conventional or digital subtraction angiography To date, 34 operations have been evaluated angiographically 6 months postoperatively. Of the three remaining patients one had an occluded graft on exploration and there were two deaths from cardiac causes.

Angiography showed that 26 (76 per cent) grafts were widely patent, 4 (12 per cent) showed moderate to severe stenosis and 4 (12 per cent) were occluded. At 12 months 25 angiograms were performed with no change in the grafts over the latter 6 months. Of the remaining five evaluable patients ultrasound demonstrated two patent grafts, two further occlusions and one patient was lost to follow-up. Although the surgical technique is technically more difficult than endarterectomy we feel that it offers major advantages.

Resection of the extracranial carotid artery in head and neck cancer surgery and for aneurysm

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We report ten cases of carotid artery resection: four as part of a radical neck dissection for cancer, and six for aneurysm. All cases had a shunt whilst restoring internal carotid blood flow using a saphenous vein graft in nine and direct arterial anastomosis in one.

The four cancer patients were Stage 4 and had recurred following radiotherapy and surgery One died at 4 weeks from secondary haemorrhage from infected paratracheal tissue, one at 6 months and one at 12 months from recurrent tumour. The fourth remains free of recurrence at 18 months.

Of six carotid aneurysms: four (three of the internal carotid and one at the bifurcation) were due to arteriosclerosis, one (internal) was due to fibromuscular dysplasia, and one (bifurcation) to idiopathic arteritis. Three of the six were symptomatic with amaurosis fugax (two) and stroke (one).

Our results show that one patient with cancer suffered a transient ischaemia attack 2 weeks postoperatively. None of the others had any neurological sequelae. Carotid pulsation was palpable, and detectable by Doppler at the latest time of follow-up (from 3 months to 3 years). Three patients with cancer who died had patent grafts at autopsy

In carotid resection, ligation of the common or internal carotid should not be undertaken as the stroke risk is unpredictable, and varies between 50 and 70 per cent in reported studies Restoration of blood flow to the internal carotid artery by end-to-end anastomosis, saphenous vein grafting or a patch is almost always possible, and should be attempted

Carotid body tumours and other cervical paragangliomas: diagnosis and management in 25 patients

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While paragangliomas of the neck are rare, the diagnosis can present considerable hazards and inexperienced removal can be disastrous. This presentation examines a personal series of 25 patients treated over an 11-year period in order to identify trends in diagnosis and management.

Between 1976 and 1986, 25 patients of median age 47 years (range 17–56 years) were referred to 1 surgeon. Fifteen were female patients and ten were male patients A total of 16 patients had single carotid body tumours, 2 had bilateral carotid body tumours and the rest had cervical paragangliomas of different origin In two patients the carotid body tumour was in association with functioning mediastinal paragangliomas. Median duration of symptoms was 3 years A total of 23 paragangliomas were resected with a zero operative mortality and a zero hemiplegia. Two required interposition vein grafts to the carotid artery and one underwent embolization before resection Histological proof of invasion of local structures by tumour was obtained in seven patients but lymph node involvement occurred in only two patients. In the 11-year follow-up only one patient died at 3 years from recurrent tumour.

Modern techniques such as IV digital vascular imaging and CT scanning allow accurate non-invasive diagnosis. Staging could be useful based on the presence of previous surgery and CT assessment of intracranial extension. Resection produces good results but may require the insertion of a carotid shunt and carotid artery reconstruction.

Stage 1 trial of clinical laser angioplasty for superficial femoral artery occlusion, using a pulsed Nd-YAG laser

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Laser angioplasty using a pulsed Nd-YAG laser has been shown in animal experiments[1] and in an artificial circulation[2] to be safe and effective. A stage I trial for critical ischaemia or in patients with severe claudication in whom balloon angioplasty had failed has been completed in 12 patients. Entry criteria specified a superficial femoral occlusion and an initial attempt at passing a guidewire mechanically was always made. Six patients received laser energy. The obstruction was passed without perforation in all six of the patients, and concomitant balloon dilatation was performed in five. Acute re-occlusion ensued in three (all occlusions > 7 cm). Of the three which remained patent, two avoided amputation and one underwent a below-knee rather than an above-knee procedure. All three vessels remained patent at 6-month follow-up and the mean arterial blood pressure index rose from 0·25 to 0·5 after treatment. Six patients did not receive laser energy Three (with occlusions > 7 cm long) underwent balloon angioplasty alone; all suffered acute re-occlusion which led to two major amputations. In two patients access to the occlusion with the laser fibre could not be obtained, and in one patient failure of the prototype laser catheter led to insufficient energy output. This patient went on to successful femoropopliteal bypass

This preliminary work shows the pulsed Nd-YAG laser to be capable of recanalizing occluded femoral arteries safely and effectively; a stage II trial in patients with less severe disease has now been started.

1. Cross FW, Bowker TJ, Bown SG. Arterial healing in the dog after intraluminal delivery of pulsed Nd-YAG laser energy. *Br J Surg* 1987; **74**: 430–5.
2. Cross FW, Bowker TJ, Marston A, Adiseshiah M, Bown SG Artificial circulation assessment of sapphire fibretips for use in laser angioplasty Vascular Surgical Society November 1986. *Br J Surg* 1987; **74**: 329

Comparative study of balloon embolectomy catheters

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This study compared the seven makes of balloon embolectomy catheter currently available in the UK, testing the most commonly used Size 4 catheters in dynamic and static experiments.

On a specially designed mechanical rig, catheters were withdrawn through a standard 6 mm lubricated transparent tube containing a fixed stenosis. Catheters of each type were tested nine times. Balloons were inflated to an initial pressure of 1000 ± 20 cmH_2O, and both the changes in pressure and the traction forces during withdrawal were measured continuously on an electronic chart recorder. The area of wall contact by each balloon was also measured. Balloon compliance varied markedly between different catheter types: the range of traction forces was 34–128 g (median 40 g) during withdrawal through the 6 mm tube, and 254–463 g (median 360 g) during passage through the stenosis.

In the second experiment, the volume of fluid and the inflation pressure required to burst balloons of each type were measured, with synchronous video recording of balloon inflation and disruption. Pressures required to burst different balloon types varied from 1240 to 1840 cmH_2O (median 1500 cmH_2O), and corresponded to the compliance of balloons observed in the withdrawal studies. Three of the seven balloon types tended to fragment when they burst.

The compliance of different embolectomy catheter balloons may reflect their potential to damage the walls of diseased arteries, while the tendency of some balloons to fragment when they burst has serious implications in clinical practice. The observations of this study may help to influence the choice of catheter for arterial embolectomy.

Screening for peripheral arterial disease in middle-aged men

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The presence of claudication in 50–60-year-old men is only 0·8 per cent when determined by questionnaire. The brachial:ankle systolic pressure index is abnormal in 4·2 per cent of middle-aged men Exercise testing could increase the detection of early disease.

A total of 100 healthy working men, mean age 55·8 ± 4·5 years, underwent a 45-min screening which included a brief history and physical examination, resting ECG, 1-min exercise test, and Vasoscan assessment of carotids and blood test.

Ten men had an abnormal exercise test, mean pressure drop 52 mmHg, and one of these also had ischaemic changes on resting ECG. Another four men had ischaemic changes on resting ECG. A single man had carotid stenosis ⩾ 50 per cent and five further men appeared to have untreated hypertension, giving a total of twenty abnormalities detected by the screening procedure. The plasma fibrinogen of the men with abnormal screens was greater (4·3 ± 0·6 g/l) than that of the remainder (3·5 ± 0·7 g/l, $P < 0·01$).

Exercise testing suggests that the prevalence of peripheral arterial disease in middle-aged men is approximately 10 per cent and other cardiovascular screening yielded a further 10 per cent of abnormalities. Raised fibrinogen levels may be a significant risk factor.

Do all patients undergoing abdominal aortic surgery require central haemodynamic monitoring?

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To test the hypothesis that central haemodynamic monitoring is unnecessary in every patient undergoing abdominal aortic surgery a prospective, randomized, controlled trial in 40 consecutive patients undergoing elective abdominal aortic surgery was carried out.

Patients with unstable angina and/or recent myocardial infarction (< 6 months) and/or left ventricular ejection < 0·50 were excluded. Intra- and postoperatively 19 patients had central venous pressure monitoring while 21 had pulmonary artery catheters inserted with wedge, pulmonary artery pressure and cardiac output monitoring.

No statistical difference appeared between the groups for age, sex, type of operation and mean ejection fraction

The following parameters were studied perioperatively: fluid balance, renal function, perioperative haemodynamics, incidence of postoperative ventilation, line complications, duration of intensive care unit and hospital stay, cardiac and major surgical complications

No complications occurred in either group. Multivariate analysis failed to show any difference in outcome for any variable in either group

These preliminary data suggest that patients with ejection fraction > 0·05 are at low risk of cardiac complications and can be successfully managed perioperatively without the potential risks and cost of pulmonary artery monitoring.

Activation of collagenase in ruptured abdominal aortic aneurysms

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The infusion of collagenase into experimental aneurysms results in aneurysm rupture. Factors which contribute to aneurysm rupture in man have not been closely described but the regulation of collagenase, which degrades medial collagen, could be important.

Collagenase was determined in media dissected from fresh aortic biopsies from patients with ruptured and unruptured abdominal aortic aneurysms by solubilization of native reconstituted [^{14}C]collagen fibrils, before and after separation from endogenous inhibitor and before and after activation with trypsin

Table *Collagenase activity of aneurysmal aorta*

	Tissue collagenase (units/g wet wt)		Secreted collagenase (units/mg protein)	
Aneurysm	Active	Latent	Active	Latent
Atherosclerotic ($n = 7$)	0·03 ± 0·02	0·16 ± 0·05	0·08 ± 0·05	0·13 ± 0·10
Inflammatory ($n = 4$)	0·09 ± 0·04	0·28 ± 0·09	0·07 ± 0·02	0·10 ± 0·06
Ruptured ($n = 5$)	0·27 ± 0·07	2·36 ± 0·24	0·95 ± 0·12	3·52 ± 0·61

Values are expressed as mean ± s.d

Collagenase activity was increased in ruptured aneurysms, this being mainly detected as latent activity after resolution of endogenous inhibitor (TIMP). In unruptured aneurysms, collagenase could be stimulated by culturing explants in medium supplemented with interleukin-1.

We propose that the augmentation of medial collagenase synthesis in response to mediators secreted by inflammatory cells is important to aneurysmal rupture.

Labelled leucocyte scanning in vascular graft infection: early results of a prospective evaluation

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It has been reported that radiolabelled leucocyte scanning may be useful in the evaluation of patients with vascular graft infection Twelve patients with a diagnosis of possible graft infection have been studied prospectively over the last 3 years All patients had indium-111 labelled leucocyte scans with gamma camera imaging after 24 and 48 h. Subsequent management was according to established surgical techniques.

Eight patients proved to have vascular graft infection and indium uptake was seen along the length of the graft in six All required subsequent graft excision, two limbs survived, three amputations were necessary and one patient died. Two patients with open wound infections and synthetic grafts had localized uptake only on leucocyte scanning; one healed with local antibiotic treatment, but the other graft required removal and was followed by amputation. Four patients, all of whom had negative scans, were not thought to have infected grafts after further investigation using digital subtraction angiography and CT scanning. These patients have been followed up for a median of 12 months (2–19 months) and have remained symptom free.

Initial experience with labelled leucocyte scanning has been encouraging, both in the diagnosis and in planning the management of patients with graft infections.

Use of Iloprost, a stable prostacyclin analogue, in the management of severe upper limb ischaemia

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An effective treatment for severe upper limb small vessel disease is required. Iloprost (Schering Health Care Limited, UK), a stable prostacyclin analogue, has been used in 19 patients with Raynaud's phenomenon (7 primary, 10 secondary, 2 hypothenar hammer syndrome) of whom 9 had digital ulceration, 4 had continuous pain and 1 pregangrene. Daily 8 h intravenous infusions, median dose 2 ng kg^{-1} min^{-1} (range 1·0–4·5), were given for 2–14 days. Response was assessed clinically, by digital Doppler score and cold stress test. In a subgroup, *in vitro* platelet aggregation was monitored during treatment.

	Outcome			
	Excellent	Fair	Slight	None
Primary Raynaud's ($n = 7$)	2	3	1	1
Secondary Raynaud's ($n = 10$)	6	4	0	0
Hypothenar hammer syndrome ($n = 2$)	1	1	0	0

Headache, flushing, nausea and vomiting were tolerated at 2 ng kg^{-1} min^{-1} in 14 patients but in 5 the dose was reduced. One patient failed to respond. Improvement was most marked in the secondary group where all digital ulcers healed. Mean follow-up is 11 months (range 2–24 months) and a gradual return of symptoms was noted from 3 months onwards. Four patients have had a further course of treatment which in all cases was successful. Doppler scores and rewarming rates tended to increase but were inconsistent. Platelet response to ADP was inhibited during infusion but postinfusion hyperaggregability was seen in some patients.

Since our results suggest that severe digital ischaemia can be successfully managed with Iloprost, a placebo-controlled double-blind trial is now under way.

Should preclotted Dacron grafts still be used?

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The initial deposition of platelets on vascular grafts *in vivo* has been correlated with clinical graft patency. We have assessed in an artificial circulation early platelet deposition on five conventionally preclotted Dacron® grafts (Bionit 2, Microvel, Triaxial, Micron, DeBakey woven) and five implantation-ready grafts (Hemashield®, Gelseal®, Hemaguard®, Plasma TFE, GORE-TEX®). Fresh heparinized human blood, containing ^{111}I-labelled platelets, was circulated for 60 min at 120 mmHg and 37°C and changes in platelet count, platelet function, and blood radioactivity were recorded. Each graft was counted for radioactivity before scanning electron microscopy of the luminal surface. The mean ($n = 8$) graft radioactivity per cm^2 divided by the mean blood radioactivity yields a graft activity index (GAI) allowing comparison of platelet deposition and thus thrombogenicity.

Implantation-ready		Preclotted grafts	
Hemashield®	2·98 ± 0·06	Microvel	35·5 ± 1·46
Gelseal®	6·55 ± 0·05	Triaxial	23·0 ± 3·57
Hemaguard®	6·95 ± 0·99	Micron	30·5 ± 8·22
Plasma TFE	2·01 ± 0·27	DeBakey	28·4 ± 2·97
GORE-TEX®	1·21 ± 0·33	Bionit 2	82·8 ± 14·6

Values are mean ± s.e.m. GAI × 10^{-2} cm^{-2} graft

In conclusion, there is significantly higher initial platelet deposition on all preclotted grafts when compared with implantation-ready grafts. Although long-term patency rates will ultimately decide their efficacy, such low early thrombogenicity and ease of use argues for the replacement of preclotted Dacron grafts by implantation-ready grafts in vascular reconstruction.

Management of unilateral iliac artery occlusion

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Between 1973 and 1987, 173 operations were carried out for unilateral iliac occlusion, 171 for primary disease and 2 for blockage of a previous aortobifemoral graft. In the early part of the series, a variety of operations including aortofemoral and iliofemoral bypass, and endarterectomy were used; femorofemoral bypass (FFB) was reserved for patients who were considered unfit for major surgery, but the results seemed so good that it became adopted as the procedure of choice. We now present the long-term results.

Over the 14-year period 140 patients underwent FFB (all but 2 having a prosthetic graft). Of these, 92 per cent had critical and 81 per cent had severe ischaemia. Nine patients cannot be traced. There were 6 early deaths (within 1 month of operation) and 11 late deaths, and the remaining 114 patients have been assessed at intervals of from 3 to 92 months, both clinically and with Doppler studies.

The cumulative patency was 86 per cent at 13 years, and 86 per cent of patients experienced subjective and haemodynamic improvement in the recipient limb. Six grafts occluded in the early postoperative phase. In five there was deterioration in the donor limb; it is suggested that the effect was due to causes other than the operation. There were two severe postoperative complications due to technical error, one of which led to early above-knee amputation

In the light of this experience, the advantages of and indications for FFB and the results to be expected from it have become clarified, and the technique standardized, so that errors can be avoided. FFB is now the operation of choice for unilateral iliac artery occlusion.

Choosing the site for lower extremity amputation in arterial insufficiency

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Successful below-knee amputation (BKA) for arterial occlusive disease leads to rehabilitation on a prosthesis more frequently than at higher levels, i e. above-knee amputation (AKA). We compare our experience of aggressive preference for BKA with the results of a national survey of amputation practice in Ireland.

A total of 55 successive amputations undertaken by us (23 BKA, 32 AKA) and their healing rates are presented. For analysis AKAs are divided into· elective AKA (AKAe), patients deemed unsuitable for rehabilitation or use of a prosthesis, and obligatory AKA (AKAo), clinical examination suggested that a BKA would not heal. Ninety-four surgeons in Ireland were surveyed by questionnaire regarding their amputation practice and success. The results are compared with our own experience.

In all, 40 survey responses (42 per cent) were obtained reporting 300 amputations. Exclusive of AKAe our distribution of cases was 23 BKA (70 per cent) *versus* 10 AKAo (30 per cent). The survey reported 41 per cent BKA *versus* 59 per cent AKAo, this is almost a total reversal. Healing in our patients for BKA and AKAo was 100 and 75 per cent and in the survey 68 and 84 per cent. Four surgeons surveyed never undertook BKA yet were responsible for 16 per cent of the total cases reported.

In most patients suitable for rehabilitation on a prosthesis we advise BKA and anticipate a high rate of healing. The survey reported a greater prevalence of AKA, thus reducing rehabilitation prospects. We recommend that the choice of amputation site for such patients be undertaken by a surgeon with experience of amputation for arterial occlusive disease

Below- to above-knee amputation ratio of 2·5:1 is the minimum acceptable standard for units providing a lower limb amputation service

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The results of lower limb amputation in the Tayside Region during the years 1981–5 have been analysed. A total of 324 major lower limb amputations were performed because of end stage peripheral vascular disease, or after unsuccessful vascular salvage procedure. The amputation level was selected on the basis of clinical judgement and the surgeons were also armed with definitive pre-operative tissue viability studies obtained from the vascular laboratory. However, initially (1981–2) the level of limb viability was determined by the above-knee systolic pressure measurement and by computerized high-resolution infrared thermograms. In 1983–5, the addition of focal radio-isotope clearance measurements allowed for calibration of the thermographic image and a precise outline of the level of viability was obtained.

Using ^{125}I-4-iodoantipyrine, a clearance value corresponding to a tissue blood flow of <2 ml 100 g^{-1} min^{-1} was deemed non-viable and blood flow was measured at three specific anatomical points

The initial below-knee to above-knee and through-knee ratio was <2, but since the introduction of the more precise pre-operative studies it has risen above 2·5 and in the last year of the study (1985) it was 2·94.

All patients who require a lower limb amputation should have pre-operative tissue viability studies, surgery performed by dedicated and experienced amputation teams and specialist postoperative rehabilitation. If these techniques are employed, a below- to above-knee amputation ratio of at least 2·5:1 is possible.

Natural history of CT-diagnosed contained aortic rupture

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During the 48-month period ending 1 January 1987, there were 250 operations for aortic aneurysm performed in this university medical centre. During this interval, 13 instances of chronic contained aortic rupture were identified in 12 patients. Contained rupture was defined as a periaortic soft tissue density in association with an aortic aneurysm in which there was discontinuity of the aortic wall. All patients were men, six were hypotensive, and four were diabetic. No patient was hypotensive before or during computerized tomography (CT) scanning. Ten of the aneurysms were abdominal; two were thoraco-abdominal Mean size of the aneurysms on CT was 7·1 cm. The periaortic soft tissue density rupture was to the left in eight and to the right in five cases Mode of presentation varied from patients with no symptoms, an incidental finding (2) to low back pain (3), abdominal discomfort (3), fever of undetermined origin (2), chest pain (1), and thigh pain (1).

Although urgent operation was advised on discovery of the condition, delay in performing surgery was actually as long as 330 days in one case, and 180 and 38 days in two others. Two of four patients with sequential CT scans showed no increase in size of the periaortic haematoma Surgical confirmation of the aortic tear was obtained in 12 aneurysms; one has not yet reached surgery. CT-diagnosed chronic aortic rupture is a recognizable and important entity that presents in a variety of ways, all of which allow optimum preparation of the patient for urgent surgical intervention. The surprisingly long history in some patients should not suggest delay in advising surgery in patients found to harbour contained aortic rupture.

Detection of superficial incompetence in venous ulceration: does it matter?

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Venous ulcers are common, affecting 1·5 per cent of those over 65 years; the accepted cause has been 'postphlebitic' due to previous deep vein thrombosis. The source and severity of venous insufficiency was investigated in 244 patients with 288 ulcerated legs by directional Doppler and ambulatory venous pressures (AVP) on dorsal foot vein cannulation

The identification of retrograde flow in deep and superficial veins after release of calf compression was possible with 4 and 8 MHz Doppler AVP recovery time in s (AVPrt) and the fall in pressure (mmHg) after ten tip-toe exercises were multiplied to give a single value for calf pump function, the pressure relief index (PRI). Improvement in PRI after occlusion of previously identified incompetent superficial veins by narrow tourniquet indicates their contribution to overall venous insufficiency. Subsequently, as a pilot study, 15 new patients with ulcers in whom PRI was doubled and AVPrt improved to >12 s were randomized to 'immediate' venous surgery and the time to complete healing of their ulcer recorded

All but 8 of 288 ulcerated legs had superficial incompetence; 3 had arteriovenous fistulae, and immobility in 5 resulted in ulceration despite normal venous function. Long and short saphenous incompetence was found in 230 (80 per cent) and 118 (41 per cent) respectively, while deep vein incompetence was identified in only 120 (42 per cent). Elimination of superficial incompetence by tourniquet resulted in functional improvement in 201 (70 per cent). Mean (±s.e.m.) time to complete ulcer healing in the seven immediate surgery patients was 24 ± 7 days compared with 75 ± 13 for eight non-operated patients ($P<0{\cdot}02$, Mann–Whitney).

Incompetence in superficial veins appears to be important in venous ulceration.

Thrombolysis in acute peripheral arterial ischaemia

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In Nottingham, 103 patients have received thrombolytic therapy for acute limb-threatening peripheral arterial ischaemia. In all, 34 patients had intravenous anisoylated plasminogen streptokinase complex, 41 patients received low-dose intra-arterial streptokinase and 28 patients were treated with intra-arterial tissue plasminogen activator (t-PA)

In the series overall, 63 (61·2 per cent) patients had limb salvage 1 month after treatment, 20 (19·4 per cent) required amputations and 20 (19·4 per cent) died. Limb salvage was more likely in patients receiving intra-arterial fibrinolytic therapy (70 per cent) and the route of administration seems more important than the agent used Significantly improved limb salvage rates (χ^2 test) were achieved in patients <70 years old ($P=0{\cdot}03$), patients with occlusions <25 cm in length ($P=0{\cdot}0001$) and patients who did not have acute critical ischaemia with absent Doppler pedal blood flow ($P=0{\cdot}0001$)

A total of 46 patients who had early limb salvage were followed for between 6 months and 3 years. Eight (17 per cent) patients had rethrombosis at the same site though only two required amputations. Seven (15 per cent) patients had amputations, mostly for continued ischaemia after failed lysis. Eight (17 per cent) patients died during the follow-up period. Continued limb salvage in this group was therefore achieved in 31 (67 per cent).

Thrombolytic therapy in acute peripheral arterial ischaemia has been shown to be successful, and to last. Its exact role is becoming more clearly defined but randomized trials are now required for verification.

Correspondence

Outlet obstruction

Sir

I was interested to read the paper by Yoshioka and Keighley (*Br J Surg* 1987; 74: 1125–9) addressing the vexed problem of whether a surgical approach is helpful in severe constipation. Outlet obstruction, defined as either inappropriate increased EMG activity in the puborectalis or failure of rectal emptying on proctography, was improved after anorectal myectomy in 54 per cent of patients whereas there was no improvement after anal dilatation However, I have certain reservations about the assessment of results of surgery in this study.

Those patients who were able to defaecate spontaneously more than three times a week after the operation were classified as having a 'good result' and the remainder a 'poor result'. These results presumably reflect reported bowel frequency rather than recorded bowel frequency It has been shown that reported frequency can be quite inaccurate when compared with objectively recorded frequency[1]. Also, patients with severe constipation usually present complaining, not of infrequent bowel actions *per se*, but rather of associated symptoms of abdominal pain and bloating, incomplete evacuation and general malaise[2].

Assessment of the results of anorectal myectomy purely on the basis of reported bowel frequency at 3 months postoperatively may, therefore, not give a true evaluation of this procedure.

The paper has, however, identified a group more likely to have a good result after anorectal myectomy. those with a short history of constipation and normal colonic transit—in other words the group least severely affected. These patients may respond to dietary and medicinal therapy without resort to surgery and the paper does not say whether this mode of therapy was exhausted before surgery was recommended.

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1. Manning AP, Wyman JB, Heaton KW. How trustworthy are bowel histories? Comparison of recalled and recorded information. *Br Med J* 1976; 2. 213–14.
2. Roe AM, Bartolo DCC, Mortensen NJMcC Diagnosis and surgical management of intractable constipation *Br J Surg* 1986; 73. 854–61.

Author's reply

Sir

In response to Mr Roe's letter, our paper refers to recorded frequency of defaecation since we acknowledge that patients often exaggerate bowel frequency. We therefore used diary cards in this study. We acknowledge that our results do not record the influence of operations on abdominal pain, bloating and general malaise. However, these symptoms became less frequent with improved bowel habit. We were impressed, however, that such symptoms were less common in patients with outlet obstruction than in those with colonic inertia. We should like to reassure readers that none of the patients were considered suitable for surgical therapy unless they had already had an exhaustive trial of dietary and medical therapy

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Surgical research in training

Sir

I read with great interest your leading articles on surgical technique (*Br J Surg* 1987; 74: 763–4) and surgical research in training (*Br J Surg* 1987; 74. 1073–4), and the letter by Matheson of Aberdeen (*Br J Surg* 1987; 74. 1190) which made special comments on both these subjects. These three contributions highlight the importance of surgical training, surgical technique and craftsmanship In the past two or three decades there has been an over-emphasis in the academic aspects of surgery both in training and in the appointment to consultancy. It is now time to stress that operative technique and skills are essential for trouble free surgery and are critical to the outcome.

In the years before the Second World War surgical technique was considered of paramount importance. At this time there were no antibiotics, no national blood transfusion service, and the knowledge of fluid and electrolytic balance was incompletely understood. In these circumstances mistakes or failure in technique resulted in high mortality and morbidity, and there was no safety net if things went wrong. In recent years, antibiotics, blood transfusion and intravenous therapy, together with the use of the intensive care unit have provided a more effective management of operative cases in both treatment and the prevention of complications. In these circumstances it is not surprising that surgical technique has lost the emphasis that it once had but which it still deserves.

A recent paper by Pettigrew and others (*Br J Surg* 1987; **74**: 791–4) concludes that operative performance is the main factor in the development of postoperative complications and confirms the adage of a former generation of surgical craftsmen who recognized that if everything went well in the theatre there were few problems in the ward Mortality and morbidity were directly related to the excellence or otherwise of the operation Since patients with surgical complications absorb a great deal of medical and nursing time in any hospital, attainment of operative excellence will reduce the strain on limited resources.

The time has come to re-emphasize the importance of surgical craftsmanship and skills This may well lead to a further analysis of the contents of programmes for higher surgical training (or apprenticeship), and to a re-assessment of the criteria for appointments to surgical consultancy

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Postoperative intra-abdominal sepsis

Sir

We were interested to read the review by Rogers and Wright (*Br J Surg* 1987, 74. 973–5) on postoperative intra-abdominal sepsis but surprised that no mention was made of the use of parenteral nutritional support. The mortality rate associated with this condition, as quoted by the authors, is high: 40–60 per cent.

We have reviewed our own figures drawn from the records of our clinical nutrition team In the first year, 115 patients were referred for nutritional support for a variety of conditions, 20 of these patients (17 4 per cent) had a diagnosis of postoperative intra-abdominal sepsis on referral. All had total parenteral nutrition in addition to drainage procedures etc as instituted by the referring surgeon; some patients had had several procedures before referral Thirteen of these twenty patients (65 per cent) survived, and seven (35 per cent) died. In the second year 28 of 144 patients had a diagnosis of postoperative intra-abdominal sepsis, again all had total parenteral nutrition, 20 survived (71 per cent) and 8 perished (29 per cent).

Our group was preselected by their referring consultant, and probably represent the severe end of the spectrum for postoperative intra-abdominal sepsis with an expected mortality rate in excess of 50 per cent. We would urge readers to consider the use of total parenteral nutrition in this situation as an adjunct to surgical drainage and antibiotics. These patients do not have a normal oral intake, are often malnourished by virtue of their pre-existing disease and are in a grossly catabolic state secondary to sepsis

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Authors' reply

Sir

Royce *et al* have drawn attention to the role of total parenteral nutrition in the management of postoperative intra-abdominal sepsis.

Our review to which they refer was an attempt to focus attention on the controversial areas of this subject We quite agree that total parenteral nutrition is an important adjunct to the management of intra-abdominal sepsis. However, we regard nutritional support, together with respiratory, cardiovascular and renal support when required, as non-controversial aspects of the intensive care of these patients, and therefore outside the scope of our article

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Oesophagectomy for carcinoma

Sir

Matthews and Steel (*Br J Surg* 1987; **74**. 1115–17) are to be congratulated for an innovative approach and their good results. I wonder however if we are confusing what we believe and what we know. the belief that cervical oesophagogastric anastomosis reduces both the risk and the consequences of anastomotic leakage is not, at least to my mind, established. In their current study 6 of 75 patients leaked and half of the leaks died—is this so different from an intrathoracic anastomosis? Why should we believe that an anastomosis in the neck will be less likely to leak than one in the chest? If the anastomosis does leak I was quite prepared to believe that the neck would be a safer place for it but a 50 per cent mortality rate for cervical leaks does not reassure me much

Of the references used in this paper Watson reported 49 patients with an intrathoracic anastomosis and 1 fatal leak. McKeown in his later paper reported 75 patients with a 2-stage procedure and thoracic anastomosis with 1 leak compared with 2 in 87 with his 3-stage technique and cervical anastomosis Keeling recently reporting results from Dublin[1] saw 15 leaks in 254 resections (all but 9 anastomoses were intrathoracic) and 9 of these leaks died; is this so different? I am quite prepared to believe that cervical anastomoses are less likely to leak and that such leaks are less dangerous but I do not think that either is established and it certainly seems to me that cervical leaks are nasty things too.

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1. Keeling P, Gillen P, Hennessy TP. Oesophageal resection in the elderly *Ann R Coll Surg Engl* 1988; **70**: 34–6

Sir

I read with great interest the paper in the December issue of *The British Journal of Surgery* by Mr H. R Matthews and Mr A. Steel. Most surgeons with experience in the surgery of carcinoma of the oesophagus would agree that the left-sided thoraco-abdominal approach is ideal for growths in the lower third It is, however, when the growth is situated in the midoesophagus that the shortcomings of the left-sided approach become apparent.

The problems presented by growths in the middle third are two: those of safe dissection at a site where the arch of the aorta gets in the way and prevents dissection under direct vision, in a situation where there are vital structures in close proximity to the growth, and anastomosis of whatever type is difficult to perform deep in the confines of the posterior mediastinum.

To meet the first problem the authors describe a procedure of freeing the oesophagus 'from behind the aortic arch by blunt dissection in the plane between the oesophageal muscle and the adjacent connective tissues thereby avoiding damage to the recurrent laryngeal nerve.' This is surely the very type of blind procedure which should be avoided especially for growths in this critical situation. As a strong protagonist of the safety of dissections under direct vision, the advantages of the right thoracic approach seem quite overwhelming, and these have been recognized for many years[1–3]. The right thoracic approach described by Ivor Lewis[2] was a critical milestone in the progress of oesophageal surgery as emphasized by R. H. Franklin[3] A further disadvantage in the technique described by Matthews and Steel is that the oesophagus is transfixed and divided in the chest, and 'the lower oesophagus is then brought down through the hiatus.' This procedure is likely to lead to infection and the possible spillage of malignant cells in the operative field. Thereafter all surgical manoeuvres are carried out in a potentially infected area.

The second problem of difficulty of intrathoracic anastomosis is solved by total thoracic oesophagectomy and performing cervical oesophagogastrostomy. This has the added advantage of wide clearance of the growth and prevention of stomal recurrence[4]. However, the left cervical approach increases the risk of damage to the thoracic duct and the left recurrent laryngeal nerve. These dangers can be avoided by a right cervical approach.

Total three-phase oesophagectomy as described by McKeown[4,6] appears to deal with these two major problems of midoesophageal growths, without the disadvantages inevitable in the technique described by the authors. They criticize the three-phase technique in the length of the operating time and 'that the operation is back to front as the abdominal part has been performed before resectability of the tumour has been established.' In response to these two criticisms it is perhaps worth pointing out that in a series of 87 total three-phase oesophagectomies, the average operation time was about 3 h, which is less than that for the technique described in the present paper. The comment that the operation is 'back to front' has only a theoretical validity and ignores certain advantages of this technique In the abdominal phase of the operation the presence of hepatic or peritoneal secondaries can be detected and precludes further major surgical procedures before the chest is opened. It also provides an opportunity for passing a guide retrogradely through the stomach and the lower oesophagus, so that a Mousseau–Barbin tube can be led through the malignant stricture with minimal trauma. So far as the right thoracic phase of the operation is concerned, it is important to note that with careful X-ray examinations of the chest combined with endoscopy and scanning techniques tumours likely to be unresectable or irremovable can in most cases be detected. Should however the growth still prove irremovable at right thoracotomy, then the mobilized stomach would prove a most appropriate means of bypass. Should extensive infiltration or fistula be present in the hilum, then the gastric mobilization can be used as part of the Kirschner–Ong procedure which has proved to be the most effective treatment of oesophagobronchial fistula.

An alternative procedure of cervico-abdominal pull-through, now referred to as transhiatal resection, was carried out by Grey Turner in 1933 (in this case a presternal reconstruction was effected) This technique has been re-introduced by Orringer[7] in 1978 The dangers of this blind procedure in extensive growths are too obvious for comment, and even in early mid-third growths the dangers of bleeding and damage to the thoracic duct render this procedure more hazardous than a well conducted thoracotomy by a team with special experience in this field

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Below-knee amputations

Sir

In response to the paper by Harrison *et al.* (*Br J Surg* 1987, **74**: 930–1) describing their experience with 38 skew flap below-knee amputations, I would like to add weight to their clinical impression of the benefits of this technique compared with the long posterior flap

In a personal series of 37 skew flap amputations over the last 4 years I have found an advantage, in terms of stump healing and mobilization, compared with 21 historical controls with the long posterior flap (though this did not reach statistical significance) in that the mean time to final limb fitting in the skew flap group was 117 days (range 30–205) *versus* a mean of 172 days (range 76–331) in the long posterior flap group Four patients in the skew flap group kept their cosmetic pylon in the long-term, partly explaining the shorter time interval. Six patients in the skew flap group (16 per cent) required above-knee conversion because of wrong level selection, early in the series. Possibly too many below-knee amputations were being attempted, but the ratio of below-knee to above-knee amputation remained similar at 51 per cent for the long posterior flap group from 1982–3, and 48 per cent for the skew flap group from 1983–7 (cf. 23·7–41·5 per cent in Harrison *et al.*'s series). Eight patients had delayed healing, but in seven healing was ultimately satisfactory In this group one patient had SLE, two fell on their stumps, three diabetics with gross staphylococcal infection required resuture, one died of renal failure and the other had persistent oedema. Thus the overall primary healing rate was 62 per cent.

I am impressed with the median time to full healing of 16·5 days in the skew flap group in Harrison *et al* 's series, but personally find it difficult to know how to compare healing times accurately—for example time to full healing might be recorded as 5 days if the wound looks healthy or 3 weeks if it does not fall apart when the sutures are removed. Length of stay in hospital, which averaged 64 days in my series, usually reflects social factors rather than healing, and the proportion of patients walking may be distorted by the inclusion of a number of bed-bound bilateral amputees who are unlikely to walk. For these reasons I think that time to final limb fitting is the most useful easily measurable variable, though it would be useful to have also a measure of rehabilitation and mobility Because of the vagaries of deliveries and transport I found that the date at which the limb was ordered to be the most reliable indicator of stump shape and healing.

Specific advantages of the skew flap technique noted were that there were no problems with the persistent indolent anterior ulcer sometimes found with the long posterior flap technique, even in the patients with delayed healing; this may be because the skin suture line does not overlie the muscle-to-periosteum suture line If the stump required revision then this could be done keeping the basic structure of the amputation intact, as previously reported[1]. In two cases with healed incisions it proved possible to use the skew flap technique without altering the shape of the flaps. With the accurate measurement and planning integral to the technique it has been easy to teach, with consistent results, and this together with the subjective evidence from the limb fitters (who feel that it produces a better shaped stump earlier) are good reasons for its adoption.

It will be interesting to see the results of the prospective randomized controlled trial, but I suspect that true matching will be very difficult, since some surgeons are likely to be more enthusiastic and better at one technique than another One of the reasons that better results are being reported, compared with historical controls, must be that increasing interest is now being shown in providing patients with a good stump, and it is more widely recognized that it is not an operation to delegate.

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1. Robinson KP, Hoile R, Coddington T. Skew flap myoplastic below knee amputation: a preliminary report. *Br J Surg* 1982. **69**: 554–7.

Pre-operative albendazole therapy and hydatid cysts

Sir
We were interested in the recent report by Dr D. L. Morris (*Br J Surg* 1987, **74**: 805–6) indicating that 4 weeks treatment with albendazole appears adequate to kill the protoscoleces within hydatid cysts, as assessed by specimens removed at subsequent surgery. Our results have been less encouraging.

Four of our patients with hydatid cysts have received albendazole at a dose of 400mg every 12h, and subsequently undergone surgery. Viability of protoscoleces in cyst fluid was determined by microscopy (for movement and flame-cell activity) and by the pepsin digestion method[1]. Two patients had viable cysts at surgery. The last patient had, in addition, received a total of over 3·2 kg of mebendazole from 1976 to 1986, and remains on albendazole at the time of writing

				Viability	
Age/ sex	Site of cysts	Diameter (cm)	Therapy (weeks)	Micro-scopy	Pepsin digestion
25 F	Abdominal, pelvic	10	4	–	–
45 M	Hepatic	14	12	+	+
35 M	Abdominal, pelvic	2	12	–	–
33 M	Spinal, paraspinal	5	7	+	+

We agree that albendazole is a promising agent against *Echinococcus granulosus*, and that its pre-operative use may make surgery much safer. Its action in such relatively short courses, however, may be to sterilize the cyst temporarily but not to kill it. It would be premature to conclude that albendazole replaces surgery as the treatment of choice for hydatid disease. Nor do we yet know for how long the drug should be given for maximum pre-operative benefit, or in an attempt to cure, when surgery is not possible.

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1. Smyth JD, Barrett NJ. Procedures for testing the viability of human hydatid cysts following surgical removal, especially after chemotherapy. *Trans R Soc Trop Med Hyg* 1980; 75: 649–52

Author's reply

Sir
The experience of Dr Davidson and colleagues is certainly most relevant; only two out of four of their cysts were dead

In our patients microscopy/eosin exclusion and gerbil intraperitoneal inoculation were used and we did find 3 out of 16 cysts to be viable. I am sure that further work is required—it is not important to establish the viability rate of untreated cysts (not all symptomatic cysts are viable). Similarly, I am sure from our *in vitro* and animal work that, whilst albendazole is active in both *Echinococcus granulosus* and *E. multilocularis*, treatment for 1 month will not kill every cyst in every patient and I would not advocate such a short course for the primary medical treatment of hydatid disease.

Apart from knowing if albendazole reduces viability of the protoscoleces within hydatid cysts in man we must address the practical problem of postoperative recurrence; any course of treatment should be simple, short and safe if it is to be remotely practical.

I am undecided on the optimal time for such prophylaxis: in the pre-operative setting the drug has to penetrate the cyst and there is often a huge amount of parasitic material present; postspillage prophylaxis has advantages in that protoscoleces in the peritoneum are much easier for the drug to reach and even 7 days postspillage therapy considerably reduces subsequent cyst formation in animals[1], but this must be given immediately following spillage[2]. Any trial of postoperative prophylaxis would need to use recurrence as its end point and as only 10 per cent will recur and perhaps not for 5–20 years this is not a trial that I can do

To date 15 patients have been entered in a UK randomized pre-operative study (untreated controls). Viability data should give us a real answer to whether it works or not. I hope that all those interested will consider entering patients so that we can resolve this issue.

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1. Morris DL, Chinnery J, Hardcastle JD. Can albendazole reduce the risk of spilled scoleces? An animal study. *Trans R Soc Trop Med Hyg* 1986, **80**: 481–4.
2. Morris DL, Taylor DH Optimal timing of post operative albendazole prophylaxis in *E. granulosus*. *Ann Trop Med Parasitol* 1988: (in press).

Erratum

'Platelet aggregation on peritoneal tube grafts and double velour grafts in the inferior vena cava of the pig', by Else B. Ribbe, B.-A. Jonsson, L. E H Norgren, S.-E. Strand and J. L. Thörne, *Br J Surg* 1988; **75**: 81–85, page 85, line 13 for 'the former authors used cranial end-to-end anastomoses' read 'the former authors used cranial end-to-side anastomoses'. We apologize for this error.

Book reviews

Hospitals. Design and Development

W. P. James and W. Tatton-Brown. 297 × 210 mm. Pp. 232. 400 Illustrations. 1986. London: Architectural Press. £49.50.

This book summarizes the postwar hospital plans for the National Health Service and represents the professional achievements and life work of W. P. James, a Department of Health and Social Services planning consultant involved in the 'Best Buy Design' with the development of a nucleus hospital concept, and W. Tatton-Brown, chief architect to the Department of Health and Social Security from 1959 to 1971. It is a difficult book to obtain but is absolutely essential browsing for a consultant surgeon over a weekend, because it shows what the architects have decided is best in the last 40 years for doctors, nurses and patients.

Architectural thinking divides hospital design into three zones: nursing (naturally ventilated); clinical (artificially ventilated); and support i.e. hotel services. They exclude in this book the nurses' home and residential beds for doctors which are off the main site. The key to good hospital planning is the manipulation of these zones and altering their relationship to produce a fully functional integrated hospital. Attempts were made to provide cheaper universal space for interchange between the zones but eventually under the pressure of cost containment the nucleus hospital was developed from 1975 onwards. This cut the costs by one third and reduced the bedspace from 75–80 to 50 or 60 m^2.

The nucleus hospital is the present flavour of the month, but an even greater landmark in architectural thinking occurred in 1955 when the Nuffield studies in the functions and designs of hospitals were published. 'An entirely new light was thrown on such things as privacy, anxiety, boredom, communication, job satisfaction and so on. A number of strongly held preconceived convictions on patient's preferences and staff priorities were upset.' From this time forward the old Nightingale ward concept of a bed placed at right angles to the window was changed to smaller 4 or 6 bed units with beds parallel to the window. The area per bed in a Nightingale ward was 20 m^2 and the new concept of smaller units with the beds parallel to the window provided up to 170 m^2 per bed in the building decade of 1965–75. The average distance for a nurse to go to a bed is 9.3 m in a Nightingale ward and longer in every other design. It is not clear whether the nurses, doctors or patients were ever asked if this new system was better than the old Nightingale ward system.

Florence Nightingale not only organized modern nursing but she influenced hospital design by working in close association with A. W. Waterhouse who became the leading hospital architect of the late Victorian era. St Thomas' was the first design based on Nightingale wards at right angles to a long corridor. The Liverpool Royal Infirmary in 1887 took the design further by combining circular wards and longitudinal Nightingale wards off a long corridor. University College Hospital in 1903, designed for a small site, placed the longitudinal Nightingale wards in a cross formation, avoiding the long corridors and moving to the concept of vertical design for the whole building rather than horizontal. All of these Waterhouse designs were founded on the basic fact that the ward for patients (the consumer) was the central important unit with the hospital beds in rows, at right angles to the windows. The ceiling was high for ventilation; the windows were sash at the bottom and tilting at the top, vertical rather than horizontal to allow more light as is well known in Victorian artist's studios; central heating was by steam; running hot and cold water was essential for modern nursing in the 1860s; and central kitchens with heated trolleys for food were firmly established for the Liverpool Royal Infirmary by Waterhouse and Nightingale.

St. Thomas' Hospital were sufficiently concerned about the new wards being worse than the old that in 1977 they commissioned the Medical Architectural Research Unit to compare a 1860 Nightingale ward with a ward in the 1960 East Wing and another in the 1970 North Wing. This report, strongly in favour of the older well tried concepts, was suppressed and not taken up as official policy, although there is a strong suspicion in this book that Tatton-Brown has seen the light in later years and wonders whether Florence Nightingale and the nurses were actually correct in the beginning.

The importance of this subject is that architecture in its present post-modern phase has moved away from the steel–concrete megalith and has reverted to a more intimate personal phase using brick combined when necessary with high technology and perhaps the time has come to rethink and design a modern Nightingale type ward 100 years later. Most surgical patients are in hospital less than a week and the average surgical ward changes over 90 per cent of its patients weekly. Do two or four or six bedded units during this short stay actually provide any more privacy than a Nightingale ward? Is 20 m^2 per bed cheaper than the small rooms? Have you ever tried reading by daylight or examining a patient in the parallel bed furthest away from the window? What do the nurses think about small rooms? What do patients prefer? What is the cost? If there is demand for a single private room should it only be provided by private health care insurance? These are all questions which are highly relevant to modern hospital design. Historically the answers were provided by the Nightingale–Waterhouse partnership 100 years ago as a response to Scutari and the Georgian country house concept of wards, changed by the 1955 report putting beds in small units and parallel to the light source, and challenged in 1977 by St Thomas', they surely should be re-assessed in 1987. This book is recommended to hospital doctors, nurses and all of us who may one day go into hospital. It is full of other information about hospitals, some relevant, some astounding.

Have more respect for corridors when you next walk down one, because they occupy 30 per cent of the building space in a hospital and 30 per cent of a new theatre suite—no wonder they are full of junk. Similarly, 30 per cent of a city's ground space is occupied by roads in the western world but less than 15 per cent in Calcutta. There should be a copy of this book in every hospital in the UK, whichever design it was built to, for comparison and search for the best design.

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Basic Surgical Practice

E. C. James, R. J. Corry and J. F. Perry. 278 × 215 mm. Pp. 587 + xvii. Illustrated. 1987. Philadelphia: Hanley and Belfus Inc. £33.00.

This book is yet another surgical text which, as the preface points out, is 'designed unabashedly' for medical students. One may legitimately ask, though, why another such book is necessary or even desirable. The authors' aim here has been to produce a text which attempts to bridge the gap between the compact condensed textbook, and the large all-embracing authoritative tome. It aims to familiarize the medical undergraduate with basic surgical tenets rather than the technical minutiae, and to identify the scientific basis and prevailing skills of the modern surgical generation.

As far as UK students are concerned, certain sections, such as parts of the 'medical records' chapter, are obviously more pertinent to American students. However, the book is comprehensive in its coverage to the extent of having a separate chapter on 'replantation of the amputated limb'. It is well illustrated with clear line drawings and the occasional X-ray and clinical photograph, but there are places in the script where several double pages of close unbroken typescript are uneased by any illustrations. This makes tedious reading in a text which is of daunting proportions to a student, with its 587 pages and 50 chapters. Of these, some cover specific organs e.g. 'the kidney', others specific diseases e.g 'myasthenia gravis', and others patient care e.g 'care of the critically ill patient'. The last ten chapters are given entirely to varying aspects of trauma.

Therefore this is indeed a comprehensive and helpful surgical text. I was disappointed in the flimsy cover which means that, if the book were to be used as the authors intended it to be, it would quickly deteriorate. The book does fulfil its aim and meet its *raison d'etre* but I am not certain that it will significantly challenge the current UK surgical texts.

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Notices and announcements

14–16 April 1988
Postgraduate Course in General Surgery
San Francisco, USA
Information School of Medicine, Room 569-U, Extended Programs in Medical Education, University of California, San Francisco, California 94143, USA

28–30 April 1988
20th Congress of the European Association for Gastroenterology and Endoscopy (EAGE)
Sirmione, Italy
Information. Professor Dr med J. M. Kimmig, Vaihinger Strasse 43, D-7000 Stuttgart 80, FRG

5–7 May 1988
Biennial Congress of the European Council of Coloproctology 1988
Geneva, Switzerland
Information. General Secretary of the European Council of Coloproctology, Policlinique de Chirurgie, Hôpital Cantonal Universitaire de Genève, 1211 Geneva 4, Switzerland

12–14 May 1988
Second Vienna Shock Forum
Vienna, Austria
Information. AUSTROPA Kongbressbüro, Friedrichstrasse 7, A-1010 Vienna, Austria

18–21 May 1988
Journées de Chirurgie Hépato-biliaire
Villejuif, France
Information: Professor H Bismuth, Hôpital Paul Brousse. 94804 Villejuif Cedex, France

20 May 1988
British Association of Endocrine Surgeons
Cardiff, UK
Information: Mr A.W. Goode, Honorary Secretary. to the British Association of Endocrine Surgeons, Surgical Unit, The London Hospital, Whitechapel, London E1 1BB, UK

23–28 May 1988
Advanced Hepato-Pancreato-Biliary Surgery
Lund, Sweden
Information Professor Stig Bengmark, Box 5003, S-220 05, Lund 5, Sweden

29 May–3 June 1988
Second World Congress on Hepato-Pancreato-Biliary Surgery
Amsterdam, The Netherlands
Information· Q. A. Laman Trip, Organizer, Alton House, Keizersgracht 792, 1017 EC Amsterdam, The Netherlands

8–11 June 1988
The Endocrine Society 70th Annual Meeting
New Orleans, Louisiana, USA
Information: Dr D. Lynn Loriaux, The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20814, USA

10–11 June 1988
3rd Steglitz Pediatric Surgical Symposium
Berlin, FRG
Information Professor Dr J Waldschmidt, Department of Pediatric Surgery, University Klinikum Steglitz de FU, Hindenburgdamm 30, 1000 Berlin 45, FRG

20–22 June 1988
7th International Workshop for the Study of Vascular Anomalies
Hamburg, Germany
Information Professor Dr D A Loose MD, Jurgensallee 44, Hamburg 52, FRG

27–28 June 1988
Serotonin Explored: what it does and how it can be manipulated for therapeutic purposes
London, UK
Information Miss Penny Robinson, IBC Technical Services Ltd, Bath House, 56 Holborn Viaduct, London EC1A 2EX, UK

29 June–1 July 1988
International Symposium on Therapeutic Progress in Urological Cancers
Paris, France
Information: Dr Saad Khoury, clinique Urologique (Pr Chatelain), Hôpital de la Pitié-83, Boulevard de l'Hôpital, 75634 Paris Cedex 13, France

3–9 July 1988
16th World Congress of the International College of Surgeons
Milan, Italy
Information. Secretariat, Clinica Chirurgica III—Universitá degli Studi, Via F Sforza 35, 20122 Milan, Italy

6–8 July 1988
Tripartite Meeting: Joint Meeting of the Surgical Research Society, the European Society for Surgical Research and the Society of University Surgeons
Bristol, UK
Information Mr DJ Leaper, Southmead Hospital, Bristol, UK

10–14 July 1988
XII Biennial Congress of the International Society of University Colon and Rectal Surgeons
Glasgow, Scotland, UK
Information. Dr H.S. Crum, Programme Chairman, Wick, Caithness, UK

14–16 July 1988
XIIIth International Update on Liver Disease
Royal Free Hospital, London, UK
Information Professor N. McIntyre, Academic Department of Medicine, Royal Free Hospital, Pond Street, London NW3 2QG, UK

14–19 August 1988
XII International Congress of the Transplantation Society
Sydney, Australia
Information: Congress Secretariat, 145 Macquarie Street, Sydney, NSW 2000, Australia

28 August–1 September 1988
Fifth World Conference on Lung Cancer
Interlaken, Switzerland
Information· Fifth World Conference on Lung Cancer, c/o AKM Congress Service, PO Box 6, CH-4005 Basle, Switzerland

30 August–2 September 1988
10th World Congress Collegium Internationale Chirurgiae Digestive
Copenhagen, Denmark
Information. Secretariat, Spadille Congress Service, Sommervej 3, DK-3100 Hornbaek, Denmark

4–8 September 1988
11th Annual Meeting of the European Neuroscience Association
Zurich, Switzerland
Information 11th Annual Meeting of the European Neuroscience Association, c/o AKM Congress Service, PO Box, CH-4005 Basel, Switzerland

6–9 September 1988
International Symposium on Computer-assisted Decision Support and Data Based Management in Anesthesia, Intensive Care and Cardio-pulmonary Medicine
Rotterdam, The Netherlands
Information. Omar Prakash MD, Erasmus University Rotterdam, PO Box 1738, 3000 DR Rotterdam, The Netherlands

7–9 September 1989
4th South-east European Symposium of Paediatric Surgery on Normal and Disturbed Esophageal Function in Childhood
Graz, Austria
Information: Professor Dr M Hollwarth, Department of Paediatric Surgery, University of Graz, Heinrichstrasse 31, A-8010 Graz, Austria

8–10 September 1988
Annual Meeting of the Association of Surgeons in Training
Belfast, UK
Information Mr Bernard Lee, Department of Surgery, Belfast City Hospital Tower, Lisburn Road, Belfast BT9 7AB, UK

12–14 September 1988
International Hepatobiliary Pancreatic Association
Nice, France
Information Dr Jean Mouiel, Department of Surgery, Hôpital Saint Roch–BP319, 06006 Nice Cedex, France

The American Journal of Surgery®

MARCH 1988 • VOLUME 155 • NUMBER 3

CONTENTS IN BRIEF

EDITORIAL OPINION

369 **Villous Adenoma.** Robert Turell

SCIENTIFIC PAPERS

370 **Successful Localization of Parathyroid Adenomas by Magnetic Resonance Imaging.** Ralph Hamilton, Burt M Greenberg, Warren Gefter, Herbert Kressel, and Charles Spritzer

374 **Therapeutic Options for Biliary Tract Disease in Advanced Cirrhosis.** Gerard V Aranha, Daniel Kruss, and Herbert B Greenlee

378 **Recurrence of Colorectal Cancer After Hepatic Resection.** Joseph G Fortner

383 **Treatment of Bowel Obstruction After Operation for Colorectal Carcinoma.** Hubert Speers, Nicholas J Petrelli, Lemuel Herrera, and Arnold Mittelman

387 **Negative Findings on Fine-Needle Aspiration Biopsy of Solid Breast Masses: Patient Management.** Robert W Painter, William E Clark, II, and Peter J Deckers

391 **Splenectomy for Cytopenias Associated With Systemic Lupus Erythematosus.** William W Coon

395 **Operation for Hyperthyroidism. Methods and Rationale.** Didier Melliere, Guy Etienne, and Jean-Pierre Becquemin

400 **Surveillance of Deep Vein Thrombosis in Asymptomatic Total Hip Replacement Patients. Impedance Phlebography and Fibrinogen Scanning Versus Roentgenographic Phlebography.** Guy Paiement, Sara J Wessinger, Arthur C Waltman, and William H Harris

405 **Acute Aortic Occlusion.** Kent H Webb and M Alex Jacocks

408 **Cholecystectomy in the Elderly.** John P Pigott and Gary B Williams

411 **A Prospective, Randomized Clinical Investigation of Cholecystoenterostomy and Choledochoenterostomy** I James Sarfeh, Eric B Rypins, James G Jakowatz, and George L Juler

HOW I DO IT

415 **Endoscopic Closure of Bronchopleural Fistulas Using a Tissue Adhesive.** John W Menard, Curtis A Prejean, and William Y Tucker

417 **Modified Technique of Sphincteroplasty With the Use of a Specially Prepared Cannula.** Antonio Guarnieri, Biagio Ravo, and Franco Moscatelli

OUR SURGICAL HERITAGE

420 **Alexis Carrel: Jules Verne of Cardiovascular Surgery.** Steven G Friedman

SURGICAL PHARMACOLOGY

425 **Plasma Expanders. An Update.** Gerald S Moss and Steven A Gould

SPECIAL COLLECTION OF PAPERS ON GASTROINTESTINAL SURGERY

436 **Trends in the Surgical Management of Duodenal Ulcer. A Fifteen Year Study.** L G Walker, Jr

439 **Gastric Disconnection in the Management of Perforated Giant Duodenal Ulcer.** Clifford A Cranford, Jr , Richard Olson, and Edward L Bradley, III

443 **A Prospective, Randomized Study Comparing Highly Selective Vagotomy and Extended Highly Selective Vagotomy in Patients With Duodenal Ulcer.** Italo Braghetto, Attila Csendes, Mario Lazo, Patricio Rebolledo, Andres Diaz, Alejandro Bardavid, Alonso Bahamonde, and Gerardo Thomet

447 **Gastrointestinal Perforation in Infants.** Anthony P Borzotta and Diller B Groff

453 **Puzzling Persistent Hyperamylasemia, Probably Neither Pancreatic nor Pathologic.** Andrew L Warshaw and Marcia M Hawboldt

457 **Value of Contrast-Enhanced Computerized Tomography in the Early Diagnosis and Prognosis of Acute Pancreatitis A Prospective Study of 202 Patients.** Pierre-Alain Clavien, Hermann Hauser, Pierre Meyer, and Adrien Rohner

467 **Cyclosporine Absorption in Apancreatic Dogs.** Kenji Kakazaki, Giacomo Basadonna, Barry Kahan, and Ronald Merrell

470 **Adenocarcinoma of the Appendix.** J Pierre Lenriot and Michel Huguier

476 **Lymphadenectomy for Cure in Patients With Early Gastric Cancer and Lymph Node Metastasis.** Takeshi Okamura, Shunichi Tsujitani, Daisuke Korenaga, Masaru Haraguchi, Hideo Baba, Yoichiro Hiramoto, and Keizo Sugimachi

481 **Carcinoma of the Cardia and Proximal Third of the Stomach. Results of Surgical Treatment in 91 Consecutive Patients.** Loik de Calan, Gerard Portier, Jean Philippe Ozoux, Bernard Rivallain, Michel Perrier, and Jacques Brizon

486 **Near-Total Gastrectomy For Gastric Cancer.** Jarmo A Salo, Ilkka Saario, Eero O Kivilaakso, and Matti Lempinen

490 **Roux-Y Stasis Syndrome After Gastrectomy.** Sven Gustavsson, Duane M Ilstrup, Peter Morrison, and Keith A Kelly

495 **Limitations and Dangers of Gastrografin Swallow After Esophageal and Upper Gastric Operations.** Sheung-tat Fan, Wan-yee Lau, Wai-chun Yip, Gah-pang Poon, Chun Yeung, and Kwok-kee Wong

498 **Colonic Interposition for Benign Esophageal Disease. Long-Term Clinical and Endoscopic Results.** Jouko Isolauri

503 **Computerized Ambulatory Esophageal pH Monitoring in 50 Asymptomatic Volunteer Subjects Results and Clinical Implications.** William G Cheadle, Gary C Vitale, Sami A Sadek, and Alfred Cuschieri

509 **Initial Control of Bleeding From Esophageal Varices With the Sengstaken-Blakemore Tube. Experience in 82 Patients** Bruno Fenayrou, Jacques Hanana, Jean Pierre Daures, and Jean Bernard Prioton

512 **Vertical Banded Gastroplasty as an Antireflux Procedure.** Mervyn Deitel, Rokesh K Khanna, John Hagen, and Rilvo Ilves

517 **Long-Term Prognosis of Patients With Severe Radiation Enteritis.** Henrik Harling and Ib Balslev

520 **Intraoperative Hemostasis and Wound Healing in Intestinal Anastomoses Using the ILA Stapling Device.** Scott Berman, Makoto Hashizume, Yeng Yang, Joseph DuPree, and Teruo Matsumoto

526 **Growth Factors and Intestinal Neoplasms.** Courtney M Townsend, Jr , R Daniel Beauchamp, Pomila Singh, and James C. Thompson

EDITORIAL COMMENTS

442 **Another View on the Management of Perforated Giant Duodenal Ulcer.** George L Jordan, Jr

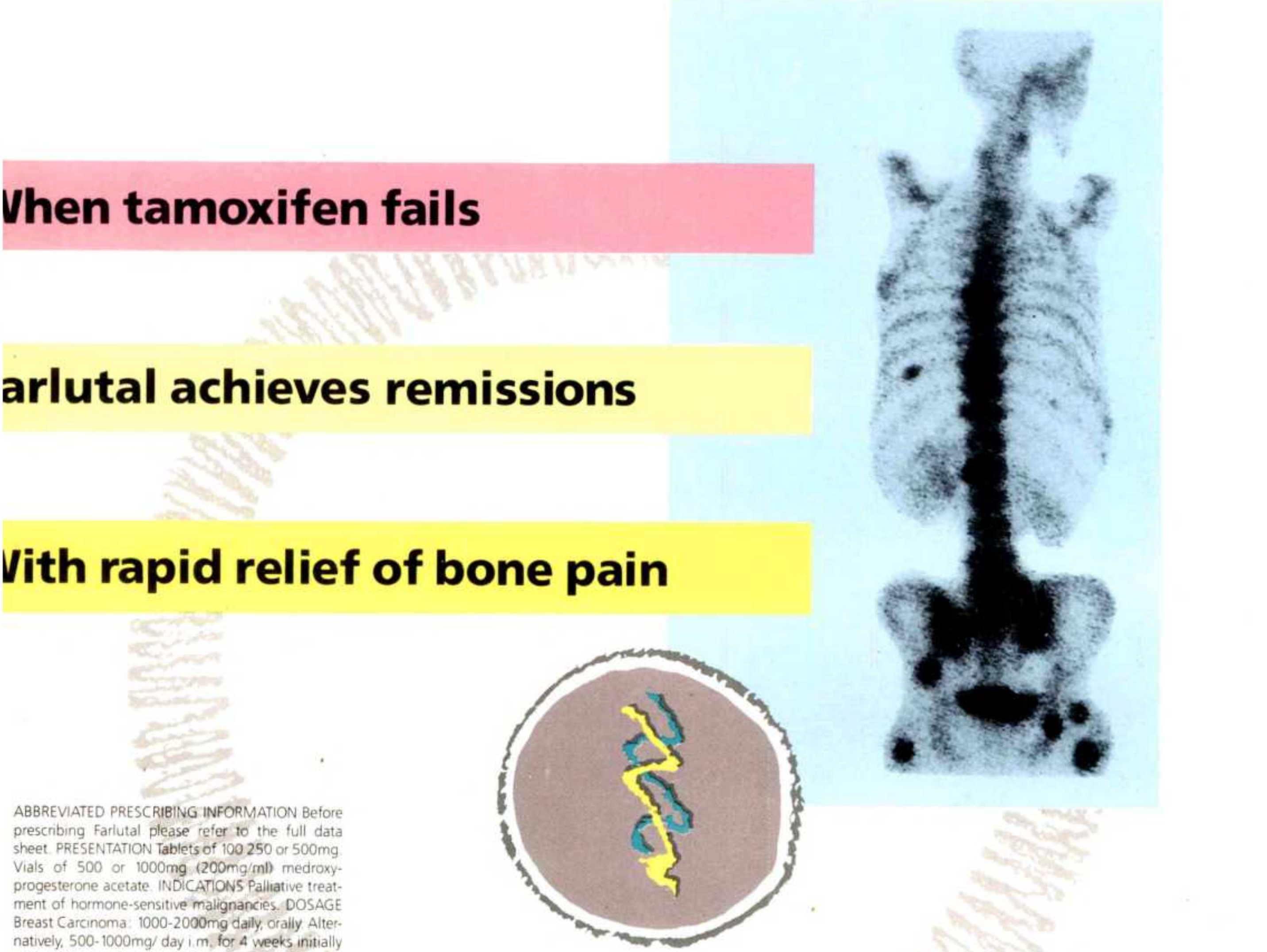
480 **Resection for Early Gastric Cancer.** Isidore Cohn, Jr

536 **What Cells, Hormones, and Nutrients Tell Cells in the Gastrointestinal Tract.** John S Spratt

A31 **Letters to the Editor**

A37 **Information for Authors**

A45 ***The British Journal of Surgery* Table of Contents (vol. 75, no. 2, Feb. 1988)**



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Volume 75 Number 5 May 1988

LEADING ARTICLES

The mammographic cancer 401
P. S. Boulter

The portal vein and colorectal cancer 402
L. P. Fielding

Assessment of injection sclerotherapy in the management of 152 children with oesophageal varices 404
E. R. Howard, M. D. Stringer and A. P. Mowat

No-touch isolation technique in colon cancer: a controlled prospective trial 409
T. Wiggers, J. Jeekel, J. W. Arends, A. P. Brinkhorst, H. M. Kluck, C. I. Luyk, J. D. K. Munting, J. A. C. M. Povel, A. P. M. Rutten, A. Volovics and J. M. Greep

New sump suction appliance for drainage of enterocutaneous fistulae 415
R. Rabinovici, P. Reissman, A. Eid, J. Berlatsky and M. Krausz

Surgical treatment of colostomy complications 416
T. G. Allen-Mersh and J. P. S. Thomson

Prognosis of colorectal cancer in the elderly 419
T. T. Irvin

Outcome of patients with rectal cancer treated by stapled anterior resection 422
L. Belli, C. A. Beati, M. Frangi, P. Aseni and G. F. Rondinara

Rigid sigmoidoscopy: an evaluation of three parameters regarding diagnostic accuracy 425
C. V. Mann, P. Gallagher and P. B. Frecker

Cerebral angiography for cerebrovascular disease: the risks 428
K. Leow and J. A. Murie

Results of excision of a cervical rib in patients with the thoracic outlet syndrome 431
S. C. W. Brown and D. Charlesworth

Inflow site: its effect on femoropopliteal and distal graft patency 434
A. Najmaldin, P. C. Clifford, A. D. Chant and J. H. H. Webster

Calf pump function in patients with healed venous ulcers is not improved by surgery to the communicating veins or by elastic stockings 436
M. C. Stacey, K. G. Burnand, G. T. Layer and Marion Pattison

Incidence of deep vein thrombosis after major abdominal surgery in Brisbane 440
P. G. Reasbeck, S. Guerrini, J. Harper, R. Sackelariou and J. F. McCaffrey

Clinical application of the cholecystokinin provocation test 444
G. T. Sunderland and D. C. Carter

Role of duodenal bile crystal analysis in the investigation of 'idiopathic' pancreatitis 450
J. P. Neoptolemos, B. R. Davidson, A. F. Winder and D. Vallance

Sphincter of Oddi dysfunction: results of treatment by endoscopic sphincterotomy 454
J. P. Neoptolemos, I. S. Bailey and D. L. Carr-Locke

Comparison of three Glasgow multifactor prognostic scoring systems in acute pancreatitis 460
T. Leese and D. Shaw

Influence of age on the mortality from acute pancreatitis 463
S. T. Fan, T. K. Choi, C. S. Lai and J. Wong

Salvage of blocked hepatic artery infusion catheters for regional therapy of metastatic liver disease (surgical workshop) 466
Jacqueline A. Goldberg, D. P. Lieberman and C. S. McArdle

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Dosage Adults: Generally 750mg t.i.d. i.m. or i.v. Severe infections 1·5 grams t.i.d. i.v. Frequency of injections can be increased to six-hourly if necessary. Infants and children: 30 to 100mg/kg/day in three or four divided doses. 60mg/kg/day will be appropriate for most infections. Neonates: 30 to 100mg/kg/day in two or three divided doses. Gonorrhoea: Single dose of 1·5 grams (2 x 750mg into different sites). Prophylaxis: The usual dose of 1·5 grams i.v. with induction of anaesthesia for abdominal, pelvic and orthopaedic operations, may be supplemented with two 750mg i.m. doses eight and sixteen hours later. In cardiac, pulmonary, oesophageal and vascular operations, the usual dose is 1·5 grams i.v. with induction of anaesthesia continuing with 750mg i.m. t.i.d. for a further 24 to 48 hours. In total joint replacement, 1·5 grams cefuroxime powder may be mixed dry with each pack of methyl methacrylate cement monomer before adding the liquid polymer.

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Surgical management of chronic pancreatitis: long-term results in 141 patients 467
Aylwyn Mannell, M. A. Adson, D. C. McIlrath and D. M. Ilstrup

Subcostal incision versus midline laparotomy in gallstone surgery: a prospective and randomized trial 473
J. C. Garcí-Valdecasas, R. Almenara, Catiana Cabrer, A. M. de Lacy, M. Sust, Pilar Taurá, J. Fuster, L. Grande, M. Pera, J. Sentis and J. Visa

Effect of drainage on subhepatic collections and respiratory function after elective cholecystectomy (short note) 476
S. T. Irwin, R. J. Moorehead and T. G. Parks

Food intake and nutritional status after total gastrectomy: results of a nutritional follow-up 477
M. Braga, W. Zuliani, L. Foppa, V. Di Carlo and M. Cristallo

Home parenteral nutrition: a review of 100 patient years of treatment in 76 consecutive cases 481
M. A. Stokes, D. J. Almond, S. H. Pettit, M. M. Mughal, M. Turner, J. L. Shaffer and M. H. Irving

Appraisal of a tissue glue in the treatment of persistent perineal sinus (surgical workshop) 484
N. S. Ambrose and J. Alexander-Williams

Experience with pancreatic banding: results of a simple technique for dealing with the pancreatic remnant after distal partial pancreatectomy (surgical workshop) 486
S. Sadek, R. Holdsworth and A. Cuschieri

Partial splenectomy for splenic cysts (surgical workshop) 488
P. M. Sagar and M. J. McMahon

Dieulafoy's erosion in the stomach as a result of an intra-abdominal vascular anomaly (case report) 489
J. W. K. Louwerens, S. Gratama, A. Zwaan and H. van der Schaar

Duodenal diverticula and jaundice: percutaneous transhepatic cholangiography may be misleading (case report) 490
A. H. Hasan, B. Moule and D. C. Carter

Gastrostomy-induced duodenal obstruction after gastric bypass (short note) 492
E. Avinoah, J. Peiser, A. Ovnat and I. Charuzi

Intestinal Kaposi's without AIDS (case report) 493
A. D. Houghton, A. R. Kittermaster and P. R. Taylor

Gluteal artery aneurysms (case report) 494
D. Demetriades, B. Rabinowitz and C. Sofianos

Choledochocele: treatment by endoscopic sphincterotomy (case report) 495
J. J. Gerritsen, A. R. Janssens and H. M. Kroon

CORRESPONDENCE 497

ERRATUM 500

BOOK REVIEWS 501

NOTICES AND ANNOUNCEMENTS 504

THE AMERICAN JOURNAL OF SURGERY (CONTENTS) (*x*)

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Cover picture

Lord Moynihan Coat of Arms

The original painting of the Arms shown on the cover of the Journal was prepared under the direction of York Herald of Arms (Conrad Swan CVO, PhD, FSA).

The young Moynihan

Berkeley George Andrew Moynihan was born in Malta on 2 December 1865. His father, Captain Andrew Moynihan VC, of Southern Irish descent, was an officer in the 8th Regiment of Foot and had served with distinction (hence the VC) in the Crimea and in India. When the infant Moynihan was 19 months old his father died of fever and his mother brought him to Leeds where his maternal family lived. He went to school at first in Leeds and then, in 1875, to Christ's Hospital on the recommendation of HRH the Duke of Cambridge, in recognition of his father's exemplary service. It was his intention to follow the family tradition and enter the Services, so in 1881 he entered the Royal Naval School, Eltham.

His mother and sister hesitated about young Berkeley devoting himself to a military career; we do not know what persuaded him but in 1883 he changed his mind and decided to study medicine and entered the Leeds school. During his medical student years Moynihan lived with his uncle, Alfred Ball, who was Superintendent of the Millgarth Street police station.

As a schoolboy Moynihan was undistinguished scholastically, his interests were swimming, football and boxing. He was an enthusiast for these sports and maintained a keenness for games throughout his life; even in his mature years he regularly went swimming, a sport which occupied his leisure hours on many long overseas surgical tours later in his life.

At medical school his indifferent academic performance ended, he became industrious and perfectionist and easily outshone his contemporaries. He rose early and went to bed early—a habit he maintained throughout life believing that what he accomplished before work really got him on. In later life all his writing and speech creating was done before he went to wards or operating rooms.

After medical school Moynihan's hankering for the Services returned and therefore, with the intention of joining the army, he did not apply for a house surgeon post; the faculty at Leeds were undeterred and appointed him house surgeon to Mayo-Robson. Again, Moynihan deferred the army and rather ungraciously accepted the house surgeon post. Mayo-Robson inbued Moynihan with a sense of zeal for surgery. Appointments as resident surgeon, assistant surgeon, surgeon, consulting surgeon and Professor of Clinical Surgery marked his progression up the hospital hierarchy. He obtained the FRCS (England) in 1890 and MS (London) in 1893.

Moynihan's long association with the Royal College of Surgeons of England began in earnest in 1899 when he was appointed examiner in anatomy for the Fellowship. In the same year he gave three Arris and Gale lectures on the anatomy and surgery of the peritoneal fossae and in 1900 a further three lectures on herniae.

The young Moynihan was robust and energetic, he was an extrovert and an easy leader, he was tall and athletic and had bright red hair. He loved an audience particularly in the operating theatre. He could entertain his guests readily and was gradually developing into an outstanding orator. Before the First War he travelled extensively to European, especially German, clinics. He soon mastered languages and became fluent in German after his first visit.

Early in his career, Moynihan realized the importance of the pen as an adjunct to the scalpel in surgical practice. He was a keen clinical observer and a prolific writer of his observations. In 1893 his first contribution 'A statistical report of surgical in-patients' appeared, in 1896 he reported in the *Lancet* the successful management of septic peritonitis following appendicitis. The year 1897 brought four major publications, 1898 five publications, 1902 fourteen papers mostly in the *Lancet* and the *British Medical Journal*, and in 1903 an output of 20 papers. His influential textbook *Abdominal Operations* was published in Philadelphia and London in 1905. Visceral and genito-urinary surgery particularly attracted his attention and hernia, gallstones, peptic ulceration, prostatectomy, nephrectomy were all subjected to his clinical scrutiny. He was lucky, the right man at the right time in the right place; he recorded what other men failed to see.

B. Devlin

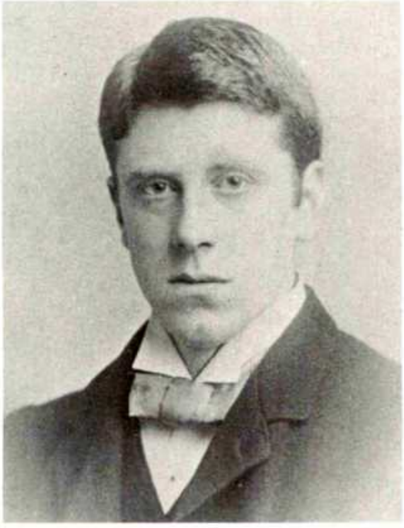

Figure 1 *The young Moynihan*

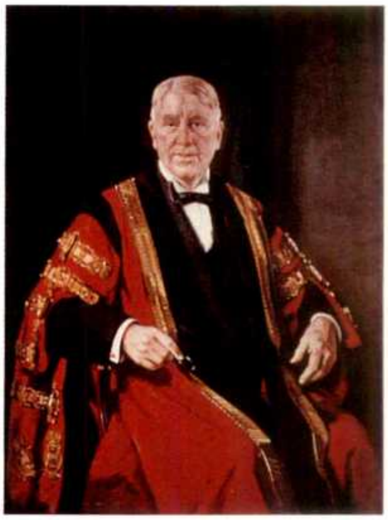

Figure 2 *Moynihan, President of the Royal College of Surgeons. A painting by Richard Jack RA, 1927*

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Further Information No suture related adverse reactions were reported during clinical trials, although a number of minor reactions were classified as being of unknown cause.

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Br. J. Surg. 1988, Vol. 75, May, 401

The mammographic cancer

A breast cancer without signs may be found at radiological investigation of symptomatic women. Screening of well women often reveals disease, as in the Guildford study of 1979–87 where 22 per cent of the cancers discovered had no physical signs. The adoption of the Forrest report by the British government will inevitably produce a spate of these lesions. Surgeons, radiologists and pathologists must be ready to cope effectively with the diagnostic and therapeutic consequences.

Mammographic cancers are characterized by radiological signs with little or no clinical abnormality. Masses, asymmetry, microcalcification and trabecular distortion may all be significant radiological pointers to the presence of disease. Considerable expertise and judgement is required to assess the degree of mammographic suspicion of malignancy and to decide the need for biopsy. The initial screening films will usually be 45 or 60° oblique views, but better spatial localization in the breast will be achieved by additional craniocaudal and true lateral views. Macroradiographs (specially magnified films) enhance the diagnostic value of these films and suspicion may be either increased or reduced; this particularly applies where microcalcification is the dominant sign. Enlarged views will often emphasize the rounded calcifications of benign microcystic disease or the ductal pattern of rods and dashes which are the hallmark of *in situ* ductal malignancy.

Physical examination is usually unrewarding but palpation is usually sharpened by knowledge that there is an underlying lesion in the breast. Ultrasound, although not a primary screening modality, plays an important part in the interpretation of dominant radiological masses—especially round or lobulated ones. The greatest value of ultrasound is the easy confirmation that a lesion is cystic rather than solid, indicating that ultrasonically directed aspiration may be possible.

When these reviewing manouevres are concluded it is time for a decision to be made about the need for biopsy. Any reasonable doubt about a lesion must be settled by the taking of a specimen for careful histological examination. This can only be achieved consistently and effectively when localization precedes biopsy. The choice between contrast dye and hooked needle methods is an individual one as both work well. The operation requires skill and attention both to the adequacy of sampling and to the resultant cosmetic appearance. Specimen radiology is mandatory and the wound is not closed until the films have been seen by the surgeon. Very careful pathological technique is needed and the judgement of 'grey area' histology is not for the tiro. Frozen section diagnosis is wholly undesirable. Surgical hunch is needed as, for instance, when microcalcification is thought to be due to ductal *in situ* carcinoma. A whole thickness and length segmental excision may be the only treatment that is needed if adequate clearance is obtained. Surgical effectiveness may be combined with good cosmesis leaving a breast that can be readily followed both clinically and radiologically.

The treatment of a mammographic cancer should be decided by a combination of pathological effectiveness and clinical safety. Obviously the management of widespread *in situ* disease or of invasive lesions may need more extensive surgery and the use of adjuvant methods such as radiation, tamoxifen or chemotherapy. No single technique can be universally appropriate given that lesions are of different size, site and differentiation and that the age of the patients may differ by several decades.

The investigation, interpretation, and management of patients with mammographically diagnosed lesions is a challenge to a cohesive team of experts who must strive to produce the lowest possible biopsy rate compatible with safety and effectiveness.

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The portal vein and colorectal cancer

It is unlikely that we will see, in the near future, any dramatic breakthrough in the overall management of colon cancer. Therefore we must increase our efforts to refine methods of perioperative management to prevent early death after surgery and diminish the incidence of local and distant tumour recurrence. Any differences in the results of treatment are likely to be small and thus well-conducted studies will be required with large enough patient numbers to prevent clinically significant advantages being lost within β statistical (type II) errors.

One such attempt is the multicentre randomized trial of operative technique reported in this volume (pages 409–415); this is a courageous attempt to tackle a difficult and controversial subject. The authors set out to distinguish between the traditional method of bowel resection (tumour first, then lymphovascular pedicle) and the 'no-touch' technique advocated by Rupert Turnbull and his colleagues[1] (lymphovascular pedicle first, then the tumour). Those familiar with the conduct of randomized controlled trials will be pleased that the authors have clearly recognized the difficulty of attempting such a comparison of surgical techniques[2]. Central to the study is the identification of the need to define the surgical methods precisely and maintain discipline within the surgical group to carry out both techniques faithfully; there was acceptance of the fact that the academic focus of some surgeons can be frail, particularly in the operating theatre. The authors deserve our admiration.

Turnbull's original results[1] have always been controversial and have never been reviewed as positively as when first presented to the American Surgical Association in 1967. Ochsner, Dunphy, Schofield, Barnes, Friesen, and Spratt all applauded the results in unequivocal terms. However since then, and with few exceptions, the results have largely been ignored.

There were two main problems with the Turnbull paper. First, there was an attempt to relegate locally advanced cases (i.e. where tumours involved adjacent organs) to a 'D' category. The reason is clear: Turnbull wished to consider only those patients in whom the draining lymphovascular pedicle could be easily identified and isolated, and not to 'mix' these patients with those in whom possible routes of spread were more complex. However, this classification also implied that patients with these locally advanced lesions were incurable and this implication has been hotly disputed. Thus, an understandable but unwise method of identifying a specific patient subset led to some general discredit for the data as a whole.

The second problem in Turnbull's paper concerned the 'control' group of cancer patients treated by conventional resection. Only 232 patients were treated by 5 surgeons over 14 years, an average of 3·3 patients per annum per surgeon! Furthermore, there was a very low rate of Dukes' A cases in the conventionally resected group (6·0 per cent) compared with the rather high rate of 15·3 per cent among Turnbull's cases. These disparities suggest that the conventionally treated group may have had a disproportionately large number of obstructed patients in whom the long-term prognosis is half that of similar cases presenting for elective treatment[3]. Despite these difficulties, there remained an important body of information showing that tumour cells both singly and in clumps could be found in both portal and systemic venous blood at the time of surgery[4–9].

Against this background Wiggers and his colleagues have conducted a carefully controlled study. They realized that the 'control' had to encompass both distribution of clinical bias, which was achieved by patient randomization, and standardization of surgical technique, which was achieved by the presence of a co-ordinating surgeon in the operating theatre. Although the authors have been modest about their data interpretation, they have produced a clinical study with long-term biological significance. Careful review of their information (*Table 5*) shows that liver metastasis occurred less frequently in eight of the twelve levels of assessment with four values being equal. Using a simple sign test, this is a statistically significant finding (two-tailed test, $P < 0{\cdot}008$)[10]. By contrast, there is no such significant pattern of metastasis to other parts of the body when conventional and no-touch techniques are compared. Furthermore, in the group of patients with angio(venous)-invasion, which occurred in no less than 26 per cent of the 235 patients, disease related deaths occurred in 8·5 per cent (10/117 patients) of the no-touch technique group *versus* 12·6 per cent (15/119 patients) of the conventionally treated group (*Table 7*). There was also a significantly longer time interval before these metastases became manifest after the no-touch technique had been used.

These data did not translate into statistically significant differences for the trial as a

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whole, probably because they have become 'diluted' with other patient subsets who are unaffected by the no-touch method and also because of the relatively small size of the trial. However, angio-invasion has been shown to be of prognostic significance in univariate analysis[11] and in more recent reports using multivariate techniques[12,13]. Wiggers' results clearly show some biological effect of the no-touch technique in some patients with angio-invasion, but the small number of patients in this subpopulation makes any statement about the possible size of the effect inconclusive. Although these differences are quite small, we should pursue them; after all, other major operations are undertaken even though the improvement in long-term survival is measurable in single figures (e.g. Whipple procedure for carcinoma of the head of the pancreas and gastrectomy for invasive cancer).

In summary, three points are worth emphasizing. First, modest gains in prognosis for colon cancer can be expected in some patients if the no-touch tumour mobilization technique is used. Second, those interested in the biology of large bowel cancer might turn their attention to the micro-anatomy and physiology of the portal vein in both its capillary beds because useful information about the metastatic process should be forthcoming. Third, if the tumour cell embolus theory has validity, then those clinical studies in which adjuvant treatment is given into the portal vein at the time of surgery might be enhanced by incorporation of the no-touch technique into the surgical methods. Perhaps surgeons and pathologists have, for too long, concentrated on lymphatic tumour dissemination despite the fact that this system leads to the thoracic duct. Most studies have concluded that wide lymphadenectomy does not prolong survival, although these studies have often involved small numbers and their conclusions have been challenged[14]. In contrast, we know that the liver is the most frequent organ for tumour recurrence from colon cancer and we seem to have very largely ignored the obvious *via naturalis* to this organ, namely the portal vein and its radicals. Anastomotic channels between lymphatics and portal venous capillaries have been described, at least in certain disease states[15], demonstrating that these two systems should not be considered in isolation.

Thus the use of the no-touch technique is supported by the positive outcome of the Wiggers' trial, the established observation of tumour emboli in the portal circulation, strong theoretical reasoning, and the lack of any increased mortality and morbidity when the technique is used. However, an increased time requirement (30 min or so per patient), a more demanding technical exercise, and surgical conventionalism place the method at a disadvantage. Nevertheless, this equation is not evenly balanced and heavily favours our adoption of the no-touch technique for colon cancer mobilization. Is it time for change?

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Assessment of injection sclerotherapy in the management of 152 children with oesophageal varices

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A total of 152 consecutive children with oesophageal varices have been endoscopically reviewed since 1979. In all, 108 of these children presented with variceal bleeding which was managed by injection sclerotherapy. Variceal obliteration was achieved in 33 (92 per cent) children with extrahepatic portal hypertension and 54 (75 per cent) with intrahepatic portal hypertension. Prophylactic injection sclerotherapy was used to obliterate large varices in 11 children with no history of haemorrhage. Bleeding episodes occurred in 38 (39 per cent) children before variceal obliteration was complete. However, the mortality rate from variceal bleeding was only 1 per cent. Complications were oesophageal ulceration (29 per cent) and stricture (16 per cent) which both resolved with conservative management. During a mean follow-up period of 2·9 years after sclerotherapy, recurrent oesophageal or gastric varices developed in 12 (12 per cent) cases, with rebleeding in 9 (9 per cent), but all responded successfully to a second course of treatment. These results are superior to contemporary surgical management and injection sclerotherapy should therefore currently be the primary treatment of choice for bleeding oesophageal varices in children.

Keywords: Portal hypertension, oesophageal varices, endoscopic sclerotherapy

Bleeding from oesophageal varices is the commonest source of serious gastrointestinal bleeding in children[1]. It is associated with a mortality rate of 5–9 per cent in children with portal vein obstruction and a considerably greater morbidity and mortality in those with cirrhosis[2]. Despite the frequency of this problem, management remains controversial, with the proponents of portasystemic shunting on the one hand[3–6] and those who favour the more conservative technique of endoscopic sclerotherapy on the other[7–10]. Problems such as shunt thrombosis with subsequent rebleeding, potential neuropsychiatric sequelae and the recognized hazards of splenectomy in young children, have lead to increasing dissatisfaction with portasystemic shunt procedures[9,11–14] These reports encouraged us to adopt and continue with treatment by injection sclerotherapy[1,7] The present series details the management and progress of 152 children with oesophageal varices, 112 of whom presented with variceal bleeding and who have now been followed up for periods ranging up to 8 years after successful variceal obliteration

Patients and methods

A total of 152 consecutive children with portal hypertension (intrahepatic 110, extrahepatic 42) and oesophageal varices have been assessed between 1979 and October 1987

In all, 112 of these children presented with variceal haemorrhage (haemetemesis and/or melaena) requiring blood transfusion on at least one occasion, and they were subsequently treated by injection sclerotherapy. Four have been excluded from further consideration in this report three foreign children with incomplete follow-up data, and one child who was referred with terminal hepatic encephalopathy and variceal bleeding in whom treatment was withdrawn soon after admission The causes of portal hypertension in the remaining 108 children (*Table 1*) were established by ultrasonography, liver biopsy, and portal venography where necessary[15]. Initial experience with 57 of these patients has already been reported[1] Compared with other series[16], there was an unusual predominance of male children 2·3:1 in portal vein obstruction and a predominance of female children 1·7:1 in intrahepatic disease.

The bleeding history in these children is shown in *Table 2*. In general, those with portal vein obstruction bled at an earlier age than those with cirrhosis, but the biliary atresia group were, on average, 3·0 years old when experiencing their first bleed. Bleeding had recurred before referral in 19 children in spite of the following surgical procedures gastric/oesophageal transection (10 patients), splenectomy (8 patients), devascularization or disconnection procedures (5 patients), central splenorenal shunt (3 patients) and portacaval shunt (1 patient) Four additional children had undergone one or two ineffective attempts at sclerotherapy

Acute variceal bleeding was initially managed by a combination of

Table 1 *The causes of portal hypertension in 108 children presenting with variceal bleeding*

Aetiology	No. of patients	Mean age at first bleed (years)
Portal vein obstruction	36	5·0 (0·7–14·5)
Biliary atresia	17	3·0 (0·5–9·3)
Congenital hepatic fibrosis	12	8·6 (2·4–12·9)
Cystic fibrosis	11	11·6 (6·0–15·0)
α_1-Antitrypsin deficiency	8	5·6 (1·3–10·3)
Choledochal cyst/other biliary cirrhosis	7	10·3 (1·7–16·0)
Chronic active hepatitis	5	6·6 (2·0–13·7)
Post-hepatitic cirrhosis	3	(6·6–7·5)
Cryptogenic cirrhosis	3	(5·5–14·7)
Wilson's disease	2	(11·0–13·5)
Familial cirrhosis	1	(13·0)
Glycogen storage disease (Type IV)	1	(6·5)
Methotrexate hepatic fibrosis	1	(12·5)
Gaucher's disease	1	(13·2)

The mean age and range is given

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Table 2 *Clinical details of 108 children presenting with variceal bleeding*

	Extrahepatic group (*n*=36)	Intrahepatic group (*n*=72)
Mean age at first bleed (years)	5·0 (0·7–14·5)	7·6 (0·5–16·0)
Mean number of bleeds before injection	3·0 (1–10)*	2·0 (1–7)
Previous surgery for portal hypertension	10	9

* Excluding bleeds before previous surgery. Ranges are given in parentheses

blood transfusion, vasopressin infusion and balloon tamponade when necessary. This was followed by endoscopy within 24 h. Sixteen patients were actively bleeding (twelve intrahepatic, four extrahepatic) when first endoscoped. All examinations were performed using a flexible endoscope (Olympus P2 gastroscope) with the patient under general anaesthesia with an endotracheal tube *in situ*. After assessment of the varices and the upper gastrointestinal tract, injections were performed via a flexible needle (Olympus NM-3KE), using 5 per cent ethanolamine oleate as the sclerosant. The injections were concentrated at the cardia and were predominantly intravariceal, paravariceal injections were occasionally used to stop bleeding from a puncture site. Approximately 2–3 ml of sclerosant were injected into each varix, to a maximum of 10–20 ml per endoscopy. At the end of the procedure residual air was aspirated from the stomach. Oral fluids were allowed 4 h later and solids on the following day.

The initial two to three treatments were performed at weekly intervals but injection was deferred for 1 week if oesophageal mucosal ulceration was present. Further treatments were given at monthly intervals until the varices had either disappeared or been converted into thrombosed cords. Regular checks were then carried out every 6 or 12 months. All cases of oesophageal stricture were managed readily by Eder-Puestow dilatation. In addition, H_2 antagonists were given to those children with oesophageal ulcers and strictures.

In all, 40 children (36 intrahepatic, mean age 7·7 years; 4 portal vein obstruction, mean age 13·5 years) have never bled from their varices, 23 of these have remained under regular endoscopic review for periods ranging from 0·2 to 5·5 years (mean 2·4 years) and 17, with prominent and extensive varices, have been treated by prophylactic injection sclerotherapy (16 intrahepatic, 1 portal vein obstruction) with a mean follow-up of 2·5 years

Results

Variceal obliteration

Of the 108 children who presented with bleeding oesophageal varices 11 are still undergoing treatment after a mean number of 4·6 (2–9) injections over 0·8 years (0·1–2·5). Of the others, endoscopically confirmed obliteration of oesophageal varices was achieved in 33 out of 33 (100 per cent) children with portal vein obstruction and 54 out of 64 (84 per cent) of those with intrahepatic portal hypertension. However, nine of the ten children whose varices were not obliterated did not complete a course of sclerotherapy because of liver transplantation (five patients) or death from liver failure (four patients). Only one child died from variceal haemorrhage, a 6-year-old boy with biliary atresia who died from uncontrolled oesophagogastric variceal bleeding despite five sclerotherapy sessions, balloon tamponade and laparotomy with direct variceal ligation. Thus sclerotherapy failed to control bleeding from oesophageal varices in only one child. These favourable results were achieved with a mean number of five to six injections over an average period of <1 year (*Table 3*).

Eleven of the seventeen patients treated by prophylactic injection sclerotherapy have had their varices obliterated after a mean number of 3·8 injections. The remaining six patients are still being treated.

Complications

The complications of injection sclerotherapy are listed in *Table 4* and apply to 565 injection sessions in the 98 children whose varices were obliterated (87 with variceal bleeding and 11 treated prophylactically). Mean follow-up since obliteration has been 2·9 years, but ranges from 0·2 to 7·8 years. Mild retrosternal discomfort and fever in the first 24–48 h after injection was relatively common. A total of 64 bleeds were recorded in 38 (39 per cent) patients before variceal obliteration was complete: 21 per cent of these occurred between the first and second endoscopies, 17 per cent between the second and third, 22 per cent between the third and fourth, 12 per cent between the fourth and fifth and 28 per cent after the fifth endoscopy. One-fifth of these bleeding episodes were due to oesophageal ulcers and the remainder were variceal. All settled with conservative treatment, but temporary balloon tamponade was required in 15 patients. Oesophageal ulceration at an injection site invariably healed but was responsible for bleeding episodes in 8 children and preceded the development of an oesophageal stricture in 16. More frequent and larger volume (>10 ml) injections more often preceded this complication but this was not statistically significant. Six children with oesophageal strictures were asymptomatic and the other ten complained of various degrees of dysphagia for solids. All strictures resolved without complication after Eder-Puestow dilatation, but three children subsequently complained of intermittent dysphagia without stricture, indicative of an oesophageal motility disturbance.

Recurrent varices

Eight children (six intrahepatic, two extrahepatic) have developed recurrent oesophageal varices after a mean interval of 2·1 (0·9–4·1) years following variceal obliteration; five of these presented with rebleeding. Furthermore, in the intrahepatic group there have been four additional rebleeds from gastric varices 0·5–3·1 years after completing treatment. All these recurrent varices have responded satisfactorily to a second course of injection sclerotherapy. In a further eight children, very small asymptomatic varices at the cardia were treated with small volumes of sclerosant and disappeared after one or two

Table 3 *Results of injection sclerotherapy in 97 children*

Results of sclerotherapy	Extrahepatic group (*n*=33)	Intrahepatic group (*n*=64)
Mean age at first injection (years)	7·8 (0·7–16·0)	8·4 (0·5–17·2)
Successful obliteration	33 (100%)	54 (84%)*
Mean number of injections to obliteration	5·4 (3–13)	6·2 (2–15)
Mean time to obliteration (years)	0·7 (0·1–2·7)	0·9 (0·1–5·0)
Mean volume sclerosant/injection (ml)	8·9	8·7

* Ten children did not achieve variceal obliteration (five transplanted, four died of liver failure and one from variceal bleeding before completing treatment). Ranges are given in parentheses

Table 4 *Complications of injection sclerotherapy in 98 children achieving variceal obliteration*

Complications of sclerotherapy	No. of patients
Bleeds before obliteration	38 (39)
Oesophageal ulceration	28 (29)
Oesophageal stricture	16 (16)
Oesophageal perforation	0 (0)
Recurrent oesophageal varices	8 (8)

Mean follow-up since completing treatment is 2·9 years. Results in parentheses are percentages

Table 5 *Results of portasystemic shunts in children from recent publications*

Authors	*n*	Mortality rate (%)*	Shunt thrombosis (%)	Rebleeds (%)	Follow-up (years)
Bismuth *et al.*[3] 1980	90 E/I	1	5·6	2	mean 4·2
Fonkalsrud[12] 1980	212 E/I	22	47	47	>5·0
Tocornal and Cruz[23] 1981	23 E	4	9	9	2–18
Alvarez *et al.*[4] 1983	76 E	0	8	>4	mean 3·6
Bernard *et al.*[24] 1985	37 I	5	11	9	mean 4·9
Heloury *et al.*[5] 1986	88 E/I	?	16	15	1–9

E, extrahepatic portal hypertension; I, intrahepatic portal hypertension. * Mortality from bleeding and surgery

Table 6 *Results of endoscopic sclerotherapy in children from recent publications*

Authors	*n*	Previous operations for PHT	Mortality rate (%)*	Rebleeds (%)	Follow-up (years)
Spence *et al.*[16] 1984	18	7	11	5·5	6·0–30
Stellen and Lilly[8] 1985	25	9	4	0	0·8–6·0
Paquet[9] 1985	59	43	0	5	0·5–10
Stray and Fausa[13] 1985	9	3	0	22	0·5–4·8
Vane *et al.*[14] 1985	13	7	0	8	2·0–4·5
Donovan *et al.*[10] 1986	16	3	6	25	1·1–6·2

PHT, portal hypertension. * Mortality from bleeding and sclerotherapy

injections. Five children (three with intrahepatic disease) developed duodenal ulcers, all occurring after variceal obliteration; four of these presented with gastrointestinal bleeding.

Mortality

There were no deaths in the group with portal vein obstruction. Thirteen of the children in the intrahepatic group died: seven from liver failure (three after completing sclerotherapy), four with cystic fibrosis from respiratory failure, one (detailed above) from uncontrolled variceal bleeding and one from a haemorrhagic gastritis following aspirin ingestion in a child whose varices were obliterated.

Surgical procedures

Before completing sclerotherapy, five children required hepatic transplants for deteriorating liver function and one child underwent laparotomy for uncontrolled bleeding (see above). After variceal obliteration, a further eight children required surgery: five received liver transplants; one required a splenectomy for hypersplenism; one underwent a splenectomy and central splenorenal shunt for a huge painful spleen; and one a splenectomy and splenorenal shunt, followed by a small bowel resection, for bleeding jejunal ulcers at the site of a previous duodenojejunostomy for duodenal atresia.

Discussion

The choice of treatment for oesophageal varices in children with portal hypertension remains controversial. Blood transfusion alone carries a mortality rate of at least 20 per cent over a period of a few years[17]. Over two-thirds of children treated by direct operations on the varices or their feeding vessels will rebleed[12,18]. Nevertheless, in adults oesophageal transection combined with a devascularization procedure has achieved variceal rebleeding rates as low as 10 per cent in a follow-up period of up to 8 years[19]. However, the mortality for elective transection is 12–20 per cent and the figure is much higher for emergency procedures[20,21]. Splenectomy alone is valueless[12,22]. Attention in recent years has focused on the relative merits of portasystemic shunting and injection sclerotherapy.

Portasystemic surgical shunts do stop bleeding, but they are associated with significant morbidity and mortality. In recent surgical series (*Table 5*) mortality rates have varied from 0 to 22 per cent and rebleeding rates from 2 to 47 per cent; these figures represent an improvement on earlier results[12,18]. Shunt thrombosis, which occurred in 6–47 per cent, particularly affected children under 10 years[25,26]. Moreover, operative morbidity in these series was not insubstantial. These results can be contrasted with those of injection sclerotherapy, shown in *Table 6*, which have yielded mortality rates of 0–11 per cent and rebleeding rates of 0–25 per cent. Furthermore, these results may be weighted in favour of surgery for two reasons. Firstly, a greater overall proportion of children with extrahepatic portal hypertension (who generally have a better prognosis) are present in the surgical series. Secondly, the latter have been more selective in their reporting: for example Bismuth *et al.*[3], who have published the best results, excluded from their analysis of 90 patients the fate of 10 other children in whom shunting proved to be technically impossible—not an uncommon finding in small children with portal vein obstruction. This group underwent variceal ligation only, a procedure known to be complicated by a high incidence of rebleeding. Similar selectivity applies to other reports[23], whereas the results of injection sclerotherapy relate to a consecutive population of children referred with variceal bleeding.

Dissatisfaction with portasystemic shunting is not only confined to shunt thrombosis and rebleeding. In children with cirrhosis, deterioration in liver function and hepatic encephalopathy are further hazards. In a recent series of 37 children, originally of Child's A or B status, 1 died in the early postoperative period with hepatic encephalopathy and 9 out of 31 children with a patent shunt developed encephalopathy during a mean follow-up period of 5 years: 3 of them died[24]. No such episodes were noted in our treated children, even in those who were Child's grade C and subsequently had liver grafts. Whilst encephalopathy may be rare in the short-term after a shunt for portal vein obstruction[27], in which liver function is usually normal, it is nevertheless a well recognized complication in the long term[22,23,28]. There are also hazards from splenectomy, performed when constructing a central splenorenal shunt or as part of the Sugiura procedure[26,29], namely late deaths from fulminating septicaemia[3,24]. A less important aspect, but one that further supports conservative management, is that the spontaneous development of portasystemic collaterals may ultimately obviate the need for any shunting procedure[9,30]. Paquet noted that 28 out of 51 children who had been prepared for shunt surgery no longer required operation when such collaterals were demonstrated on pre-operative angiography[9]. Finally, previous intra-abdominal surgery compounds the difficulties for the transplant surgeon which must be considered since liver transplantation is becoming increasingly successful for children with chronic liver disease.

Several prospective randomized controlled trials have now been conducted in adults comparing sclerotherapy with shunt surgery[31]. In one study, sclerotherapy proved as effective as portacaval shunting in the acute management of variceal haemorrhage[32]. Another trial compared the distal splenorenal (Warren) shunt with endoscopic sclerotherapy in the long-term management of variceal bleeding[33]. Although sclerotherapy had a higher rebleeding rate, it was associated with significantly better liver function and an improved survival when used as the primary treatment. Moreover, it does not reduce portal perfusion or carry the risk of encephalopathy. No randomized controlled trials have been performed in children.

What then are the relative merits of injection sclerotherapy? Since its introduction more than half a century ago[34], injection sclerotherapy has proved to be an effective method for controlling recurrent haemorrhage from oesophageal varices. It was first reported as a successful technique in children in 1959[35]. However, the technique was overshadowed by the development of portasystemic shunt surgery and it was not until renewed interest was stimulated by results in adults[36,37] that it was again advocated in children. Little more than 200 children have been reported as having had injection sclerotherapy to date. We have previously published our early experience with sclerotherapy[1,7], confirming both its safety and efficacy, and now report a much larger series with longer-term follow-up.

Endoscopically confirmed obliteration of oesophageal varices was achieved in less than a year in all children who completed a course of treatment, 19 of whom had rebled after previous unsuccessful surgery for portal hypertension. Such surgery features prominently in other sclerotherapy series in children[8,9,14]. Sclerotherapy was effective in extrahepatic or intrahepatic portal hypertension, even in infants. The mortality from variceal bleeding in this series was 1 per cent, the single death from uncontrollable haemorrhage before variceal eradication was complete. Such favourable results are possible if children needing treatment are concentrated in centres where the necessary expertise can develop. Further follow-up is still required to assess longer-term effectiveness, particularly since 19 per cent of adults bleed from recurrent oesophageal varices within 6 years of endoscopic obliteration[38].

Endoscopic sclerotherapy is associated with a variety of complications[2]; in particular, oesophageal ulceration and stricture formation. An oesophageal stricture probably arises from a combination of chemical oesophagitis and acid reflux, supporting the use of H_2 antagonists in these cases. No stricture was severe enough to warrant surgery and all resolved after repeated dilatation. Most ulcers were asymptomatic and were only detected because of regular endoscopy; they are an inevitable temporary consequence of the sclerosant[39,40]. They more often follow frequent or large volume injections[41], but may additionally be related to the depth of injection[42]. Changes in treatment intervals[43] and assessment of other sclerosants[44] may reduce the frequency of these problems. Some studies have suggested an advantage from intravariceal injection, but a paravariceal technique can certainly produce good results[9] and radiological contrast studies have indicated that these procedures are not distinct[45].

Three children almost certainly have an oesophageal motility disorder producing intermittent dysphagia. Manometric and pH studies in adults before and after sclerotherapy have revealed lower oesophageal dysmotility, reduced lower oesophageal sphincter tone and reduced clearance of refluxed acid[39,46]. There were no instances of oesophageal perforation in this series—now a rare complication with the use of fibreoptic endoscopes. Other serious complications, such as spinal cord paralysis[47], mediastinitis[48], septicaemia[49], broncho-oesophageal fistula[50] and cardiac tamponade[51], which have been rarely reported, did not occur in this series. Endoscopic sclerotherapy does have the disadvantage of repeated general anaesthesia which can lead to a deterioration in lung function in patients with cystic fibrosis[52]. Intensive perioperative physiotherapy, bronchodilators and prophylactic antibiotics are used in these children in an effort to minimize any deleterious effects.

Gastrointestinal bleeding before variceal obliteration was complete was relatively common and of similar frequency to that reported in adults[43]. The source was usually a non-thrombosed varix but in one-fifth of cases it was from oesophageal mucosal ulcers. However, this complication was less common after the first few injections. Bleeding following variceal obliteration was due either to other pathology such as peptic ulceration or recurrent oesophageal or gastric varices which developed in 12 (12 per cent) patients. Peptic ulceration as a source of haemorrhage needs prompt recognition to avoid inappropriate treatment directed at portal hypertension[14]. The problem of recurrent varices has justifiably concerned some authors[10,53] but it was reassuring to discover its low incidence during a mean follow-up period of 3 years and that these cases have so far been successfully managed by a further course of sclerotherapy. The treatment of small asymptomatic varices at review endoscopies may further reduce this problem[8].

The value of prophylactic injection sclerotherapy is uncertain: recognizing the morbidity associated with gastrointestinal bleeding and having experienced 1 death from acute bleeding uncontrolled by sclerotherapy, we used this in 17 patients all of whom had prominent and extensive varices from chronic liver disease. Controlled studies in adults have yielded conflicting results[54,55]. There is little evidence for such treatment in extrahepatic portal hypertension in particular since some of these patients never bleed[22,53] and we do not support prophylactic portasystemic shunting advocated by some authors[4,56].

In conclusion, endoscopic sclerotherapy with an associated mortality from bleeding of 1 per cent and a rebleeding rate of <10 per cent appears to be the current treatment of choice for the primary management of oesophageal varices in children. This applies to both children with primary intrahepatic disease in which the underlying liver disease determines the prognosis, and those with portal vein obstruction in whom variceal bleeding is the main threat to life. These results are better than primary contemporary surgical management which should probably be initially reserved for those patients without ready access to skilled endoscopy facilities or who bleed from intestinal varices. Longer term follow-up studies are still needed to monitor recurrence and any late morbidity, to determine the optimum interval between endoscopies which, together with technical developments, may help to minimize ulceration and stricture, and to reduce the frequency of bleeding from varices before complete obliteration.

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No-touch isolation technique in colon cancer: a controlled prospective trial

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In order to assess the effect of the no-touch isolation technique, in the treatment of large bowel cancers, on the site of first recurrence and disease-free and overall survival, 236 patients were prospectively and randomly assigned to either the no-touch isolation technique (117 patients) or to a conventional resection technique (119 patients). No patient with distant metastases or unresectable disease entered the study. The two treatment groups were comparable with regard to patient characteristics. Pre- and postoperative complications (including mortality within 30 days) were similar in both groups. After a complete follow-up of 5 years, a tendency for reduction in the number of, and time to, occurrences of liver metastases was seen in the no-touch isolation group (P=0·14). *This effect was most obvious in the sigmoid colon with angio-invasive growth. Overall* (P=0·42) *and corrected* (P=0·25) *survival did not differ significantly among the treatment groups although in every analysis the survival data of the no-touch isolation group were superior. The data do suggest a limited benefit of the no-touch isolation technique. This observation is important since the morbidity and mortality of surgery were equal in both groups.*

Keywords: Colon cancer, no-touch isolation technique, liver metastases

Surgery offers the best possibility for cure in colon cancer, which is achieved in approximately 50 per cent of patients. Adjuvant chemotherapy has not been able to prolong disease-free survival[1] and radiotherapy is of limited value in rectal cancer either as a primary[2] or as an adjuvant therapy[3]. Despite an increased resectability rate and a diminished postoperative death rate, overall 5-year survival figures have improved only slightly during the last 40 years[4,5].

Surgical therapy consists of removal of the primary tumour in combination with segmental resection of the adjoining normal bowel, including the mesentery and, if necessary, any adjacent organs invaded by the tumour. The first aim of surgery is to relieve the patient of his complaints (such as blood loss or bowel obstruction) but, secondly, the possibility of local recurrence after the resection should be minimal and no further dissemination should be caused by operation. Although surgical resection seems to be a standard procedure, the extent of local resection, the necessity for and the extent of lymph node dissection, and the effectiveness of measures preventing local or systemic spread during operation are not well defined[6].

Several investigators[7–9] have identified malignant cells, in particular in cell clumps due to tumour manipulation[9], in the portal blood of patients with colon carcinoma. In experimental models the intravenous injection of tumour clumps is more effective than the injection of solitary tumour cells in the production of distant metastases[10]. The establishment of such micrometastases is enhanced by surgery[11] and anaesthesia[12]. Although this effect may be influenced by immunosuppression[13], other biological changes such as hypercoagulability[14,15] may play a part.

The first description of lymphovascular ligation before mobilization of the cancer-bearing segment in colon cancer, in the hope of reducing peroperative dissemination to the liver, was given by Barnes in 1952[16]. The name of Turnbull[17] has been definitively connected with this technique because he was the first to provide promising clinical data using the so-called 'no-touch' isolation technique in colon cancer and report that it reduced the frequency of cancer cells found in the portal blood[18]. Opponents[19,20] of this technique attributed his results either to patient selection or to the introduction of a new staging system and claimed similar results as a consequence of extended resection only (*Table 1*).

The aim of the present study was to evaluate, by means of a prospective controlled study, the effect of the no-touch isolation technique in colon cancer and to define its position as a standard means of colon resection. Both survival and the number and location of the recurrences were studied with particular attention being paid to possible differences in the development of liver metastases.

Table 1 *Comparative absolute 5-year survival rate in cancer of the colon*

Stage	Turnbull *et al*[17] (Cleveland)	Stearns and Schottenfeld[19] (Memorial)	Enker *et al.*[21*] (Chicago)
With lymph node involvement	57·9%	52·2%	56·5%†
Resection undertaken for cure	68·9%	69·3%	65·3%
All stages	50·9%	NS	52·8%

NS, not stated, *rectum included, †cases with 1–4 lymph nodes involved were not included

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Patients and methods

Eligibility criteria and randomization

Patients were eligible for the study if they fulfilled the following criteria.

(1) histological proof of carcinoma in the pre-operative biopsy or a radiological lesion suspected of malignancy;
(2) distal margin of the tumour located at least 8 cm from the anal verge allowing sphincter-saving resection;
(3) no evidence of distant metastases or locally unresectable advanced disease:
(4) no previous malignancy in the preceding 5 years except for basal cell carcinoma of the skin;
(5) general condition sufficient to allow resection therapy.

Patients were excluded from study if.

(1) acute resection had to be undertaken because of perforation;
(2) previous surgery for this carcinoma had been undertaken except for the construction of a diverting colostomy,
(3) multiple colonic carcinomas were present;
(4) bad compliance for follow-up was anticipated

Patients were randomized pre-operatively through central registration either to a conventional resection technique or to the no-touch isolation technique.

Surgical therapy including quality assurance

In order to compare the effect of lymphovascular isolation only, no special attempts were made to perform extended lymphatic dissection During conventional resection the first step of the operation, after inspection and palpation of the liver and para-aortic lymph nodes, consisted of the mobilization of the tumour-bearing segment This was performed before any vessels were ligated.

The principles of the no-touch isolation technique were observed in the theatre from the time of opening the abdomen. The cancer-bearing segment was inspected without palpating it After identification, the lymphovascular bundles were selectively ligated and divided. The artery had to be sacrificed in this phase as the first step, preventing venous overflow to the marginal arteries. Secondly, the marginal vessels and the bowel lumen, proximal and distal of the tumour were ligated Details of the technique for the different locations are described in a protocol, according to the guidelines of Jagelman and Turnbull[22].

Operations were performed by both surgeons and surgical trainees. During the first year and part of the second year of the trial every no-touch operation in all the participating hospitals was assisted by a member of a group of staff surgeons from the central university hospital, thus ensuring a standard procedure without violation of the no-touch principles.

Localization

Tumours of the caecum and ascending colon were classified as right-sided tumours. Tumours of both flexures were included in the transverse colon. Left-sided tumours comprised those in the descending colon and sigmoid colon All tumours below the sacral promontory were classified as rectosigmoid in this study

Pathology

In all cases, the original diagnosis made by the local pathologist was centrally reviewed regarding stage, grade and angio-invasive growth. Staging was done according to the Dukes' classification. Strict criteria were employed for grading[23] Available haematoxylin and eosin sections were studied for at least 20 min for the presence of angio-invasive growth.

Patient follow-up

A standard computerized follow-up program was instituted which delivered the necessary forms monthly for each patient. The frequency of the follow-up was every 3 months during the first year and every 6 months thereafter At 5 years the patient's status regarding disease-free survival and overall survival was evaluated and registration of follow-up was stopped. Every evaluation consisted of a history, physical examination, blood examination (including haemoglobin concentration, liver function, and carcino-embryonic antigen (CEA) level). Every year, or when indicated, an ultrasound or isotope scan of the liver, chest X-ray, and colonoscopy or barium enema were undertaken Neither radiotherapy nor chemotherapy were allowed as adjuvant therapy.

Criteria for recurrence

If possible, histological or cytological evidence was obtained to confirm metastatic or recurrent disease. Characteristic changes on chest X-ray, repeated liver scan or abdominal CT scan, preferably in combination with a raised CEA level, were also accepted. Abnormal liver function tests or a raised CEA level without a strongly suspected anatomical site were not accepted as proof of recurrent disease. Recurrence was considered local if it occurred in the primary tumour bed or adjacent organs. Carcinomas were classified as new if there was a distance of several centimetres from the suture line. If close follow-up according to the preset criteria was no longer possible, the patient was classed as lost to follow-up with a disease-free interval up to the last day of adequate evaluation. The patient was, after that date, still evaluable for survival because it is possible in the Netherlands to obtain this information via the patient's general practitioner, in combination with the death records of the registration services

Statistical analysis

All patient data were recorded in the computer A χ^2 analysis for association was used for interpretation of the cross-tabulations between the patient characteristics and the two treatment groups For comparison of numbers the median of age and size of the tumour was used.

After the exclusion of postoperative deaths (defined as death within 30 days after the operation) life tables were calculated for disease-free interval. Life tables for survival were calculated, excluding postoperative death, both for absolute and disease-related death rates. The life tables were computed with the BMDP program (Biomedical Computer Program P-series)[24], using the product limit method of individual survival times (Kaplan–Meier)[25]. Comparison of treatment groups with respect to disease-free period and survival were made by means of the log rank tests[26] and by means of the score test after adjusting for differences in distribution of patient characteristics (summarized in *Table 2*) by means of proportional hazards regression. The proportional hazards regression model was also used to test for treatment–prognostic variable interactions. a significant result possibly indicating a preferential treatment for certain prognostic categories

Results

Patient characteristics

Between January 1979 and February 1982 a total of 304 patients were entered by 8 participating centres. In order to have proper supervision by a limited group of surgeons from the central university hospital, randomization had to be performed pre-operatively. Forty-eight patients were withdrawn during the operation. After exploratory laparotomy (without palpation of the tumour) liver metastases were apparent in 22 patients. Extensive advanced local tumour growth, determined by inspection and necessitating mobilization of the tumour as a first step to assess resectability, excluded another 26 patients. Postoperatively 20 patients were found to be ineligible because either no malignancy was found (12 patients) or more than one carcinoma was discovered in the resected specimens (8 patients). These cases appeared to be equally distributed among the treatment arms (*Table 3*). Thus 236 patients remained for the final analysis, 119 in the conventionally operated group and 117 in the no-touch isolation group.

Patient-related variables were similar between the two groups (*Table 2*) except for sex distribution. CEA levels were not determined for all patients. The median values pre-operatively were 4 4 ng/ml for the conventional group (84 observations) and 3·6 ng/ml for the no-touch group (83 observations). One month postoperatively the values in the no-touch group were insignificantly higher (2·8 ng/ml) than in the conventional group (2 2 ng/ml); the numbers of observations were 66 and 69 respectively. The CEA levels did not differ significantly among the two groups. All these known prognostic data confirmed an equal balance between the two protocol arms despite the withdrawals. There were also no significant differences in randomization over the several institutions regarding treatment arm, stage and complications (data not shown, but available on request).

Morbidity and mortality

No significant differences were observed for mortality and morbidity between the two treatment groups (*Table 4*). Six

Table 2 *Comparability of the two treatment groups*

Characteristic	Conventional (%)	No-touch isolation (%)	*P*	Total
Total patients	119	117		236
Sex				
Male	46 (38·7)	60 (51·3)	0·05	106
Female	73 (61·3)	57 (48·7)		130
First symptom				
Blood loss	34 (28·6)	39 (33·3)		73
Change bowel habits	25 (21·0)	20 (17·1)		45
Ileus	4 (3·4)	4 (3·4)		8
Other	56 (47·1)	54 (46·2)	0·82	110
Duration of symptoms				
<2 weeks	13 (11·4)	9 (7·8)		22
2 weeks to ≤2 months	31 (27·2)	36 (31·3)		67
>2 months	70 (61·4)	70 (60·9)	0·58	140
Tumour location				
Right-sided	29 (24·4)	29 (24·8)		58
Transverse	15 (12·6)	13 (11·1)		28
Left-sided	49 (41·2)	43 (36·8)		92
Rectosigmoid	26 (21·8)	32 (27·4)	0·77	58
Dukes' classification				
A	30 (25·2)	26 (22·2)		56
B	53 (44·5)	54 (46·2)		107
C	36 (30·3)	37 (31·6)	0·86	73
Grade				
Well	18 (15·4)	8 (7·0)		26
Moderate	90 (76·9)	94 (82·5)		184
Poor	9 (7·7)	12 (10·5)	0·12	21
Angio-invasive growth				
Absent	89 (75·4)	85 (72·6)		174
Present	29 (24·6)	32 (27·4)	0·63	61
Age (years)*	70·0	68·0	n.s.	
CEA pre-operatively†	4·4	3·6	n.s.	
CEA postoperatively†	2·2	2·8	n.s	
Size primary tumour (cm)	4·0	4·9	n.s	
Distal free margin (cm)	6·2	6·9	n.s.	
Number of resected lymph nodes	3·8	4·8	n.s	

CEA carcino-embryonic antigen level; n.s., not significant, * median; † upper limit of normal 5 ng/ml. Some patients are not included in the table

Table 3 *Status of the patients in the study*

	Conventional	No-touch isolation	Total
Patients randomized	150	154	304
Withdrawals before resection	21	27	48
Postoperatively ineligible	10	10	20
Patients analysed	119	117	236

Table 4 *Complications according to treatment*

Variable	Conventional	No-touch	*P*
Total patients	119	117	
Peroperative complications			
Blood loss >1 litre	3	4	
Faecal spill	4	7	
Tumour spill	2	2	0·24
Postoperative complications			
Wound infection	15	10	
Septic complications	3	2	
Suture dehiscence	4	4	0·64
Mortality			
Survived <30 days	3 (2·5%)	4 (3·4%)	n.s
Survived <60 days	5	6	

n.s., Not significant

patients in the no-touch group died within 60 days of the operation, four due to septic complications, one from anaphylactic shock and another from a cerebrovascular accident. In the conventionally operated group, two patients died within 60 days of septic complications but two other patients died respectively 3 and 4 months after the primary operation as a late result of sepsis. The other patients dying within 60 days of conventional operation died as a result of myocardial infarction, rupture of a cerebral aneurysm and an acute severe bronchospasm. The overall mortality within 30 days was 3·0 per cent and the total death rate as a direct result of the operation was 4·7 per cent.

Recurrent disease

At the time of analysis all patients had a follow-up of 5 years after surgery. In the no-touch group, 8 of 111 patients (excluding postoperative deaths) had no reliable follow-up at 2 years regarding disease-free interval and in 7 more cases data were lacking at the end point of the study. For the conventional group these figures were 10 of 114 at 2 years and another 8 patients had no reliable data at the end point of 5 years. Of the 236 patients, 74 suffered from recurrent disease (including 6 metachronous carcinomas) according to the preset definition. Tumour recurrence according to site and pathology between treatment did not differ significantly (*Table 5*). However, the observed figures for the number of liver metastases were 22 in the conventionally operated group and 14 in the no-touch group. There was a slight tendency for an increased number of

Table 5 *Recurrences according to the initial site and pathology among the treatment groups*

Variable	Conventional			No-touch isolation			Grand total
	Liver	Elsewhere (incl. local)	Total	Liver	Elsewhere (incl. local)	Total	
Total	22	18	40	14	20	34	74
Localization							
Right	5	5	10	4	2	6	16
Transverse	2	6	8	2	4	6	14
Left.	11	4	15	4	8	12	27
Rectosigmoid	4	3	7	4	6	10	17
Angio-invasive growth							
Absent	14	11	25	10	11	21	46
Present	8	7	15	4	9	13	28
Dukes' classification*							
A	4	2	6	1	1	2	8
B	8	8	16	8	9	17	33
C	10	8	18	5	10	15	33
Grade							
Well	2	0	2	0	2	2	4
Moderate	17	15	32	12	16	28	60
Poor	2	3	5	2	2	4	9

* One patient not assessed

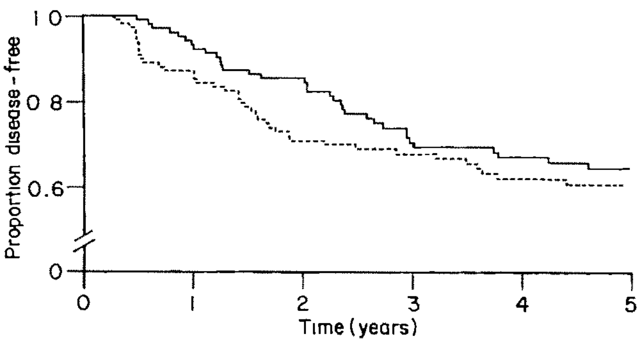

Figure 1 *Relationship between resection technique and time to tumour recurrence regardless of site. ——, No-touch isolation, ----, conventional*

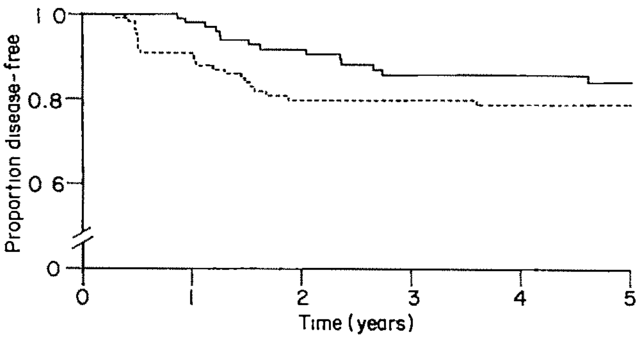

Figure 2 *Relationship between surgical technique and time to recurrence in the form of liver metastases only ——, No-touch isolation, ----, conventional*

liver metastases in the conventionally operated group in cases with an advanced sigmoid carcinoma and when angio-invasive growth was present Estimates of the probability of time to recurrent disease, for all failures is plotted in *Figure 1* (log rank test $P=0{\cdot}34$, score test 0·18). However, the difference in liver metastases as evidenced by the recurrence distributions (*Figure 2*) was not statistically significant (log rank test $P=0{\cdot}14$, score test 0·10). Not only were there fewer liver metastases in the no-touch group, they also tended to occur later at a median of 22·4 as opposed to 12·6 months (*Figure 3*).

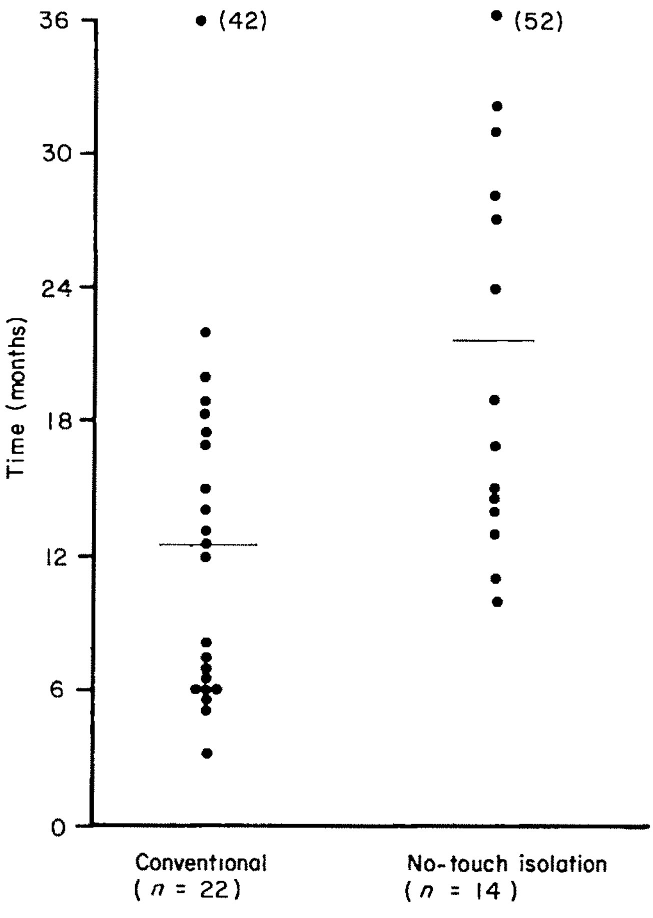

Figure 3 *Relationship between surgical technique and the timing of detection of liver metastases*

Six patients (three in both groups) developed a new metachronous carcinoma far from the suture line.

Survival

Of the 236 patients in this analysis, 66 have died as a result of their colon cancer: 37 in the conventionally operated group and 29 in the no-touch isolation group. No patients were lost to

Table 6 *Deaths according to treatment arm*

	Conventional ($n=119$)	No-touch isolation ($n=117$)	Total
Death due to recurrent disease	37 (31 1)	29 (24·7)	66
Death due to other causes (including postoperative)	15	18	33
Lost to follow-up	0	0	0
Total	52 (43·7)	47 (40·1)	99

Values in parentheses are percentages of the total number of patients in each treatment arm

Table 7 *Disease-related deaths among the treatment arms according to localization of the primary tumour and classification of angio-invasive growth*

Variable	Conventional	No-touch isolation	Total
Localization			
Right	11	6	17
Transverse	6	5	11
Left	14.	9	23
Rectosigmoid	6	9	15
Angio-invasive growth			
Absent	22	19	41
Present	15	10	25
Dukes' classification			
A	5	2	7
B	17	13	30
C	15	14	29

follow-up regarding survival. Figures for disease and non-disease related death are presented in *Table 6*. There were differences in distributions of death rates over categories of prognostic variables between the treatment groups (*Table 7*). For example there were 15 deaths in the 29 patients (52 per cent) with angio-invasive growth treated by conventional operation as opposed to 10 deaths in the 32 patients (31 per cent) with angio-invasive growths treated by the no-touch technique. Although in every analysis there is a slight advantage for the no-touch group, life table analysis failed to discover significant differences when the two treatment arms were compared both for the total number of deaths (log rang test $P=0{\cdot}42$, score test 0 30) and the disease-related deaths (log rank test $P=0{\cdot}25$, score test 0·19) (*Figure 4*).

Discussion

Two hundred and thirty-six patients with primary colon carcinoma, without evidence of distant metastases, were enrolled in this prospective study to evaluate the effectiveness of the no-touch isolation technique in colon cancer[16,18]. Survival data were compared with Turnbull's results[17,27,28] Criticisms[19,20] of his data may be summarized as follows: the introduction of a new staging system may have allowed shifting of stages, patient selection may have occurred especially with reference to the control group, specific data on the mutual proportions of local recurrence and distant metastases are lacking, the technique may have resulted in an extended lymphadenectomy, and it is noteworthy that positive results were obtained in cases with lymph node metastases only. In addition to these criticisms, increased morbidity and mortality might occur as a result of ischaemic bowel ends causing suture line breakdown and from damage to ureter or duodenum. Since the present study was concerned with the effect of lymphovascular isolation, before mobilization of the tumour-containing bowel segment only, no extended lymphadenectomies were performed. The equal distribution among the two groups with regard to the length of resected bowel and the number of resected lymph nodes supports the contention that the extent of lymphadenectomy was similar.

In interpreting the results of the present study one should carefully consider some of its limitations In order to allow quality control of the operation by a limited number of surgeons experienced in this technique, randomization had to be performed before all eligibility criteria could be fulfilled. This caused withdrawals after exploratory laparotomy during which, on some occasions, liver metastases or locally advanced tumour were discovered. Theoretically it would have been better if the envelope was opened after reaching the stage of the operation where the difference in technique had to commence[29]. The exclusion of patients (20 in both groups) because no malignancy was found or two tumours were discovered in the resected specimens seems to be of less importance. An extensive comparison (*Table 2*) between the two treatment groups was performed to justify the similarity of the treatment groups. Both patient- and surgeon-related variables[30] seemed equally distributed. This was especially reassuring in the case of those factors known to be very strong prognostic variables such as staging[1,23] and CEA levels both pre- and post-operatively[31–33]. The major drawback of this kind of study is the impossibility of defining minimal disseminated disease before resection is undertaken. Even palpation of the liver during operation is not always correct and although new generations of CT scans[34] are able to detect smaller metastases it is still impossible to detect masses smaller than 0·5 cm.

The application of the no-touch technique did not cause an increase in morbidity. Pre- and postoperative complications were also equally distributed between the treatment groups. The postoperative mortality rate of 3·4 per cent following no-touch resection was similar to that of the control group and to the 2·2 per cent from Turnbull *et al.*'s data[17]. Of course this percentage is lower than that reported when resection for all stages is undertaken. Mortality rates for curative resections only are hardly reported in literature but should be below 5 per cent. The fear of an increased incidence of suture line leakage (four in both groups) as a result of an inadequate blood supply, caused by early vascular ligation, appeared to be unfounded. Blood loss during operation was not consistently recorded in our series but in one report from the Lahey Clinic[35], it was reported as less than that associated with techniques in which the tumour is mobilized as the first step of the operation. This gain may by itself be worthwhile since adverse effects of blood transfusions have been described recently[36].

Differences in disease-free survival distributed over the various sites of recurrence are the best way of evaluating the effect of this therapy. However, exact localization of all metastatic disease is impossible. Survival can be easily and

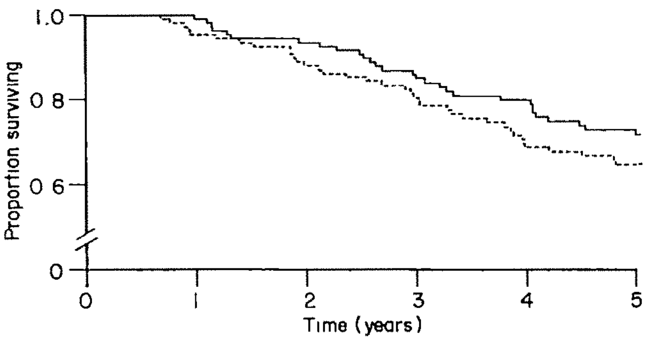

Figure 4 *Relationship between surgical technique and disease-related death* ——, *No-touch isolation*, ----, *conventional*

reliably registered for all cases, but is itself inaccurate because of deaths unrelated to the disease and the treatment of metastatic disease, although ineffective in colorectal cancer, is not reflected in these calculations. Evaluation of death unrelated to disease and overall survival did not result in substantial differences. Although the trial did not prove of significant benefit to the patients in the no-touch isolation arm, in all analyses the no-touch group had superior results. The reduced number of liver metastases with similarity for incidence at all other sites of recurrences, and the late time of occurrence of the liver metastases in the no-touch group are of interest. This reduction of liver metastases was observed particularly if the tumour was situated in the sigmoid area. It is reasonable to attribute this difference to the following mechanism. Complete vascular isolation, preventing outflow of tumour cells during operation, is difficult to achieve. Experiments in dogs have shown an increased overflow via the marginal vein if the central vein was ligated before the occlusion of the artery[37]. The inconstant vascular anatomy in the transverse colon (including both flexures) and the impossibility of achieving complete ligation of the distal marginal vessels in the rectosigmoid area make these areas, on theoretical grounds, not very suitable for this technique. This presumption is supported by our data since no difference in the incidence of liver metastases is seen in the case of patients with tumours of the transverse colon and rectosigmoid. The left colon is more suitable for both central ligation and disruption of the marginal flow. The fear that overflow to the central circulation may follow occlusion of the central draining vein with a resulting increase in lung metastases because of portacaval shunting[38] was not confirmed by longer follow-up in the study of Morgan[39] and in the present study. The reduction in the number of liver metastases in patients undergoing the no-touch technique and who had angio-invasive growth is an important observation since the occurrence of liver metastases is strongly related to angio-invasive growth[40]. This effect was even more strongly reflected in the survival curves in which the negative effect of angio-invasive growth on survival disappeared in the no-touch group. No effect in this regard was observed for the presence or absence of lymph node metastases. Although plausible, it remains speculative to attribute this phenomenon to the reduction of dislodged tumour clumps passing to the liver. It is also possible that massive embolization during surgery is responsible for the observed early occurrence of liver metastases in the conventionally operated group. The influence of tumour factors, liberated by manipulation, on already present deposits is another possible explanation for the differences in incidence and time of detection of the liver deposits.

The absolute 5-year survival in both the no-touch and conventionally operated groups is high, namely 59·8 per cent and 56·3 per cent respectively. This is in accordance with the results of several series advocating a certain technique[18,20,21,41] and with the results in both the control and treatment arms in the prospective series of the GITSG[1]. This high survival rate is probably a result of patient selection. It is however the basis of a strong plea for a control group in these kind of studies[1,42].

In summary, in this study we have not observed the difference in survival rates as reported by Turnbull. However, the no-touch isolation technique is a neat and simple technique once learned, and did not result in an increased morbidity or mortality. Furthermore, in all the analyses the results showed a tendency in favour of this technique. Although outcome of the disease may already be determined at the moment of diagnosis, every attempt should be made to prevent worsening of the prognosis during operation. The only remarkable differences are the lower occurrence of liver metastases in patients with carcinomas in the sigmoid area and in cases with angio-invasive growth. It is our opinion that this technique should be used for all tumours in areas where it is easily applicable. Even small improvements in prognosis are valuable in this disease with its high incidence and when other types of adjuvant therapy are not available.

Acknowledgements

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Surgical workshop

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New sump suction appliance for drainage of enterocutaneous fistulae

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We have developed a new sump–suction appliance with which to maintain effective drainage of fluid from enterocutaneous fistulae while maintaining skin protection.

A Stomahesive* flange with a central opening is placed on the skin. A Jackson–Pratt flat suction drain, cut to the size of the external opening, is carefully introduced into the fistula (*Figure 1*). The drain is secured to the Stomahesive ring with a 3/0 silk suture. The distal tube of the drain is then passed through a urostomy bag, but not before three holes are cut in it in order to drain occasional fluid which might accumulate in the bottom of the bag. A suction tube is connected directly to the bag so that the distal part of the drain tube is within its lumen. The bag is fastened to the Stomahesive and the suction tube is connected to a suction system with a collecting bottle located below the patient. Venting is created by inserting a 19 gauge needle into the suction tube.

We have found that this system, composed of cheap and easy available components, allows optimal control of enterocutaneous fistulae without skin excoriation. The device requires minimal care, saves the patient a lot of inconvenience, and has no complications.

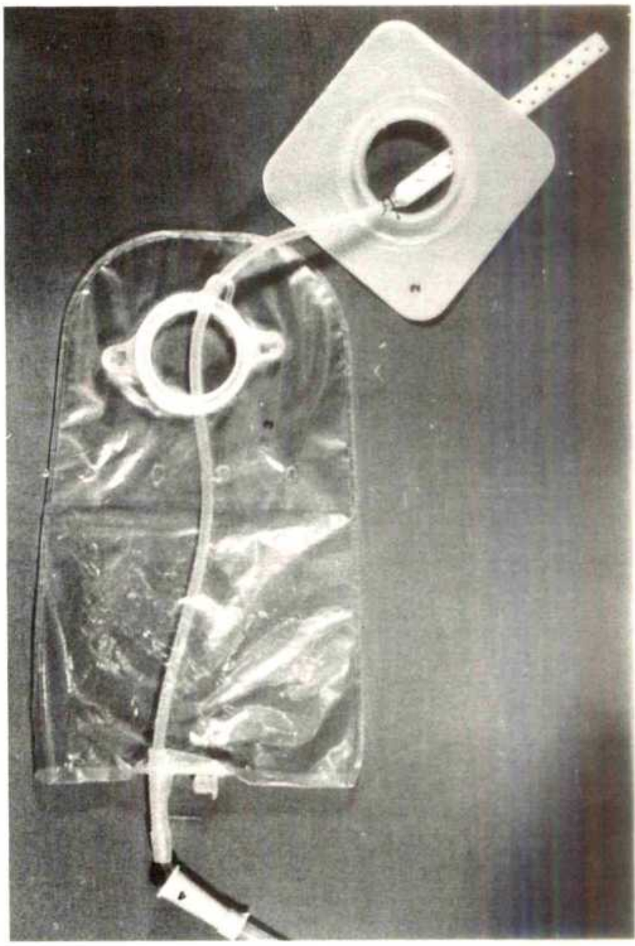

Figure 1 *The sump–suction appliance is composed of a Stomahesive flange, urostomy bag and a Jackson–Pratt flat suction drain*

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Surgical treatment of colostomy complications

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One hundred and twenty-three patients (M:F, 0·9:1; mean age 62 years) underwent 156 operations between 1954 and 1984 for correction of late colostomy complications (stenosis 65 patients, prolapse 16 patients, paracolostomy hernia 42 patients). Sixty-three per cent of patients eventually had a good result but in some up to 5 operations were necessary. Local excision of scar tissue at the mucocutaneous junction was associated with a 61 per cent (43/71) success rate for relief of colostomy stenosis. Where local fixation failed to prevent recurrent colostomy prolapse (13/20, 65 per cent of local fixation operations), colectomy and ileostomy was the most effective second procedure (2/3, 67 per cent success rate). Where local repair of a paracolostomy hernia failed (15/32, 47 per cent of local operations), resiting of the stoma to the umbilicus or right side of the abdomen produced better results (3/7, 43 per cent success rate) than resiting to another trephine on the left side of the abdomen (2/14, 14 per cent success rate).

Keywords: Colostomy, complications, surgical treatment

Although restorative resection of the rectum is now the most frequent treatment for rectal carcinoma, complete excision of the rectum and anal sphincters is still necessary in at least 11 per cent[1] of patients with rectal carcinoma. Although 70 per cent of patients with a colostomy adapt well to their stoma within a year of rectal excision, complications related to the stoma and surrounding skin affect 50 per cent of patients[2]. Complications following end sigmoid colostomy occur both early in the immediate postoperative period and later, at any time after stoma formation. Late complications are usually the result of stenosis, prolapse or paracolostomy hernia.

There have been few reports of the outcome of surgical correction of these complications and, in some cases, both patient and stoma nurse may be asked to cope with a troublesome stoma when revision might offer relief. The aims of this study were to assess the feasibility and results of surgical correction.

Patients and methods

The case notes of all patients who had undergone excision of the rectum with end sigmoid colostomy and who underwent revision of the colostomy, in one hospital between 1954 and 1984, were reviewed. Results of stoma revision were classified as: good, where the complication was cured; moderate, where the complication or another complication returned but no further surgery was deemed appropriate; poor, where the complication or another complication returned such that further surgery was necessary. Statistical analysis of differences in results between treatment subgroups was not attempted since the size of subgroups was too small to allow valid analysis. Differences in age, weight, and interval to treatment between subgroups were assessed by grouped Student's *t* test.

Results

A total of 123 patients (M:F, 0·9:1; mean age 62 years) underwent 156 operations between 1954 and 1984 for correction of late colostomy complications. The number of each type of complication treated, and the pattern of their association with each other is shown in *Figure 1*. Colostomy prolapse was associated with paracolostomy hernia in 50 per cent of patients in whom colostomy prolapse occurred. One hundred and seventeen (75 per cent) operations represented first attempts at repair, 23 (15 per cent) were second, and 16 (10 per cent) were third or subsequent attempts. The proportion of patients undergoing more than 1 attempt at repair was higher for colostomy prolapse (8/16, 50 per cent), than for stenosis (12/65, 18 per cent) or paracolostomy hernia (8/42, 19 per cent).

The incidence of stenosis treated by surgical revision, among 1678 patients undergoing rectal excision for cancer between 1954 and 1984, declined from 3·03/100 colostomies in the decade after 1954 to 2·04/100 colostomies in the subsequent decade, whereas the incidence of colostomy prolapse and hernia undergoing surgical revision increased between 1954 and 1984 (prolapse from 0·35 to 2·48/100 colostomies; hernia from 1·52 to 2·48/100 colostomies). Median interval between raising the stoma and onset of complication was 1 year (range, from 1 month to 32 years). Although there was a wide range (*Figure 2*) in the interval between raising the stoma and development of these complications, the median and 50 per cent range were greater for paracolostomy hernia than for either stenosis or prolapse (*Figure 2*).

Results of surgical treatment are given in *Table 1*. The cumulative chance, with each successive attempt at correction, of achieving a successful result is shown in *Figure 3*.

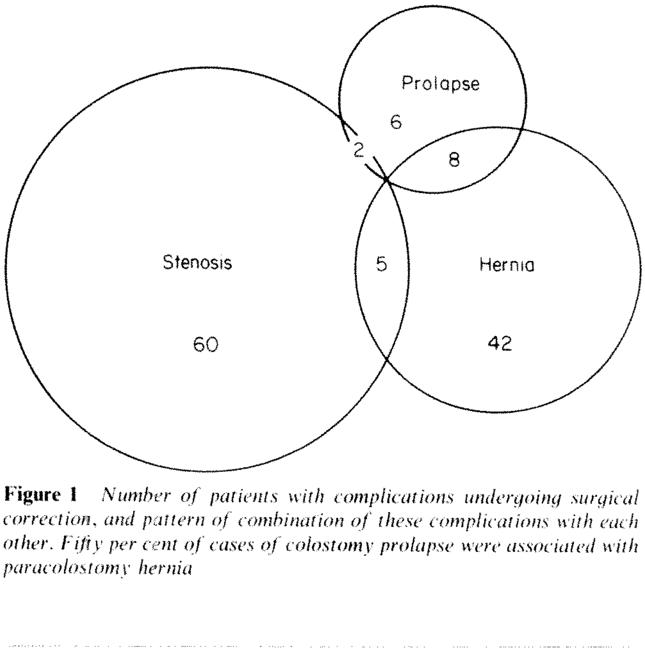

Figure 1 *Number of patients with complications undergoing surgical correction, and pattern of combination of these complications with each other. Fifty per cent of cases of colostomy prolapse were associated with paracolostomy hernia*

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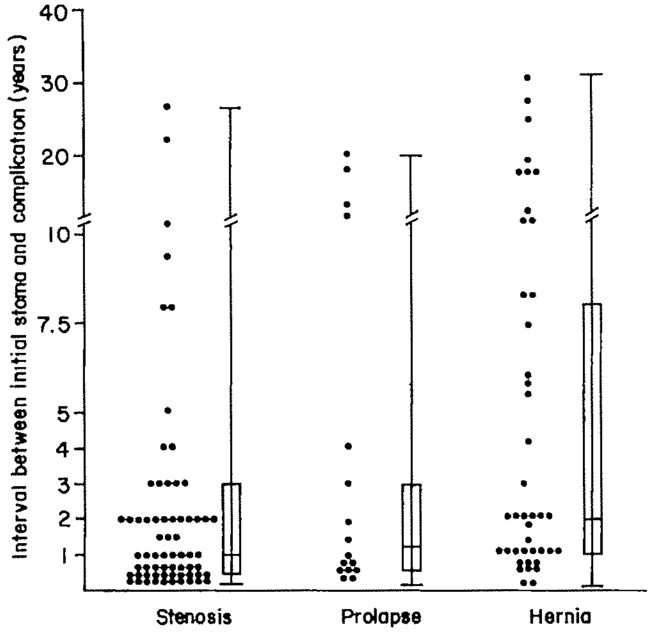

Figure 2 *Interval between raising the stoma and development of symptoms from colostomy complication. 'Box and whisker' format—the whisker outlines the range, the box encloses 50 per cent of the variation and the horizontal line indicates the median*

Table 1 *The results of 156 operations for the repair of late colostomy complications*

Operation	Result Good	 Moderate	 Poor
Stenosis			
Local (n=71)	43 (61)	15 (21)	13 (18)
Resite stoma (n=3)	2 (67)	1 (33)	—
Prolapse			
Local resection and fixation (n=20)	7 (35)	2 (10)	11 (55)
Resite stoma (n=6)	2 (33)	1 (17)	3 (50)
Colectomy with ileostomy (n=3)	2 (67)	1 (33)	—
Paracolostomy hernia			
Local repair (n=32)	17 (53)	3 (9)	12 (38)
Resite stoma above and medial (n=14)	2 (14)	1 (7)	11 (79)
Resite stoma to umbilicus or right side of abdomen (n=7)	3 (43)	3 (43)	1 (14)

Values in parentheses are percentages

Stenosis

Sixty-five patients with colostomy stenosis underwent seventy-four correction operations (mean 1·1, range 1–3 operations/patient). Seventy-one (96 per cent) operations involved local excision of scar tissue surrounding the mucocutaneous junction, with mobilization of the colon to the abdominal wall or, occasionally, peritoneal cavity. The stoma was resited in three (4 per cent) patients with recurrent stenosis. Overall, the probability of achieving a good result was 69 per cent (45/65) after up to 3 operations (*Figure 3*). Reasons for failure in the remaining 20 (31 per cent) patients were recurrent stenosis (10/65, 15 per cent), paracolostomy hernia (9/65, 14 per cent) and prolapse (1/65, 2 per cent). There was no significant difference in the interval to repair between patients having a good result (4·5±7·7 years) and those who did not (4·7±7·8 years). There was also no significant increase in mean age at time of repair among patients who had a good result (63·6±12·2 years) compared with those who did not (59·6±17·7 years).

Prolapse

Twenty-nine operations for control of colostomy prolapse were carried out in 16 patients (mean 1·8, range 1–5 operations/patient). In 20/29 (69 per cent) operations this took the form of a local mobilization of the colostomy to the peritoneal cavity, resection of redundant colon, and fixation of the colon and its mesentery to the lateral parietal peritoneum. Good results were achieved in 7/20 (35 per cent) operations. There was no significant difference in the interval between stoma formation and prolapse in patients having a good result (7·7±10·9 years) and those who did not (5·5±4·5 years). There was also no significant difference in age at time of prolapse repair between patients who had a good result (58·8±12·6 years) compared with those who did not (58·3±14·5 years).

In patients with recurrent prolapse, the proportion of patients having a good result from resiting the stoma (2/6, 33 per cent) was less than that among patients who had undergone colectomy and ileostomy (2/3, 67 per cent). The cumulative proportion of good results, after up to 5 operations (*Figure 3*), was 69 per cent (11/16). Reasons for failure in the remaining 5 patients were recurrent prolapse (2/16, 12 per cent), paracolostomy hernia (2/16, 12 per cent) and retraction (1/16, 6 per cent). One patient who developed a paracolostomy hernia associated with prolapse was treated by Marlex mesh (C.R. Bard Inc., Massachusetts, USA) repair which resulted in peristomal skin sinuses

Paracolostomy hernia

Forty-two patients underwent 53 paracolostomy hernia repairs (mean 1·3, range 1–3 operations/patient). The interval between raising the stoma and paracolostomy hernia repair was significantly (t=11·8, P<0·001) longer in patients who had a good result (11·3±9·4 years) compared with those who did not (7·2±6·1 years). There was no significant difference in age at time of repair between those who had a good result (65·2±12·7 years) and those who did not (63·7±13·2 years). There was also no significant difference in body weight at time of repair between those having a good result (70·4±9·4 kg) and those who did not (72·7±17·5 kg). The most frequent operation—hernia reduction and local repair of the paracolostomy defect with non-absorbable sutures—was successful in 53 per cent (17/32) of cases.

Among patients with large or recurrent hernias, the proportion of good results was higher when the stoma was resited to the umbilicus or right side of the abdomen (3/7, 43 per cent) than when it was resited on the left side of the abdomen above and medial to the previous stoma (2/14, 14 per cent). The cumulative proportion of good results after up to 3 operations (*Figure 3*) was 52 per cent (22/42). Reasons for

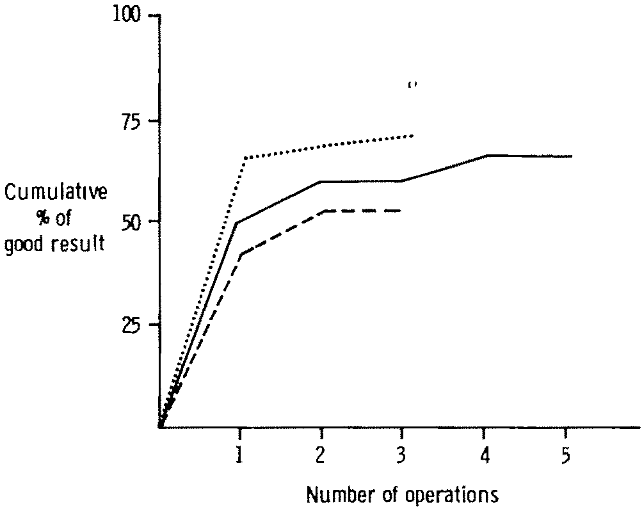

Figure 3 *Cumulative proportion as percentage of good results achieved by number of operations performed ....., Stenosis, ——, prolapse, – – –, hernia*

failure in the remaining 20 patients were recurrent hernia (10/42, 24 per cent), retraction or stenosis (7/42, 17 per cent) and prolapse (3/42, 7 per cent).

Discussion

Estimates of the prevalence of late colostomy complication increase with length of follow-up[3,4]. Some degree of paracolostomy hernia is found in 60 per cent of patients with a colostomy whereas stenosis and prolapse are less common[5]. Indications for surgery, except in the unusual case of a strangulated paracolostomy hernia or ischaemic colostomy prolapse, are based on a judgement of the degree of inconvenience experienced by the patient balanced against fitness for operation and probability of achieving a successful result. Frail or grossly obese patients have therefore been excluded from the present series since such patients would be regarded as unsuitable for colostomy revision. In a previous study reported from St. Mark's Hospital[5], 67 per cent of patients with colostomy stenosis, 20 per cent with prolapse, and 13 per cent with paracolostomy hernia underwent surgical revision.

In the present study, neither age nor increased body weight were associated with fewer good results. Thus, in this selected population of patients considered suitable for operation, there was no evidence to support the view that age or obesity should be regarded as a contra-indication to stoma revision. Shorter time interval between raising the stoma and operation for paracolostomy hernia was associated with fewer good results. This may be because early-onset paracolostomy hernia is more likely to be associated with a hernia-prone abdominal wall than when appearance of the hernia is delayed.

Causes of the rise in incidence of prolapse and paracolostomy hernia undergoing surgery cannot be determined from the present study. Possible reasons include: greater willingness in more recent years to repair these complications; increased identification of complications, particularly paracolostomy hernia which may develop long after colostomy formation (*Figure 2*); and changes in surgical technique used when raising the stoma. Techniques for raising a colostomy which avoid paracolostomy hernia or prolapse have not, to our knowledge, been described. However, the decline in the incidence of patients with colostomy stenosis undergoing surgery, noted between 1954 and 1964, may result from the introduction of mucocutaneous suture at the time of raising the colostomy. This was first advocated in 1951 by Patey[6]. Before this the end of the colon was left free above the abdominal skin where the serosa tended to granulate and stenose[7].

Local excision of scar tissue around colostomy stenosis produced good results in the majority (61 per cent) of cases, and an overall success rate of 69 per cent was achieved in correcting colostomy stenosis. Treatment of colostomy prolapse was less satisfactory. Local resection and fixation was successful in only 35 per cent of cases. Where this failed, resiting the stoma with a further resection did not greatly add to chances of achieving a good result (33 per cent). Colectomy with ileostomy provided better results (67 per cent success rate) in recurrent prolapse The tendency to colostomy prolapse did not extend to the ileostomy in these patients.

Paracolostomy hernia was diagnosed later after stoma formation than either stenosis or prolapse. It has been suggested[8] that the risk of paracolostomy hernia is reduced if the colostomy is sited within the rectus sheath. In the present study, resiting of the trephine to within the rectus sheath—above and medial to the previous stoma—was successful in only 14 per cent of cases. Better results (43 per cent) were achieved, in these more refractory cases, by resiting either at the umbilicus or to the right side of the abdomen. Therefore when resiting of the stoma is necessary, it should be moved either to the opposite side of the abdomen or to the umbilicus. Rectal excision in patients whose stoma was resited to the umbilicus was via paramedian incision. The effect of previous midline incision on subsequent stoma resiting to the umbilicus is not known. Encouraging experience with repair of paracolostomy hernia using Marlex mesh has been reported[9,10]. This was attempted in only one of our patients, and the mesh became infected. However mesh infection is reported[11,12] as being infrequent if the skin incision is kept away from the stoma.

With attention to blood supply, tension, stoma siting and mucocutaneous suture[7,8,13], complications arising from technical error should be avoided. However, a colostomy is an unnatural protrusion through the abdominal wall, and some complications (particularly paracolostomy hernia) may be inevitable[7]. Correction of these complications can be difficult and, even after multiple operations, may be unsuccessful. However, results from this study suggest that where a complication making the stoma difficult to manage does occur, surgical revision can offer relief to the majority of patients in whom it is attempted. Advances in sphincter-saving surgery have not eliminated the need for permanent colostomy, nor have advances in stoma care eliminated the need for colostomy revision. More attention should be given to recognizing, and devising surgical techniques for preventing and correcting, these troublesome problems.

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Prognosis of colorectal cancer in the elderly

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The prognosis of colorectal cancer in the elderly was examined in a study of 306 consecutive patients. The patients were divided into two groups: Group 1 included 171 patients of average age 77 years (range 70–97); Group 2 comprised 135 patients of average age 59 years (range 22–69). There was no significant difference between the two groups with regard to the mode of presentation, the location and Dukes' classification of the tumours, the incidence of palliative operations, and the perioperative mortality. The surgical mortality rates in Group 1 were 6 per cent overall, 4 per cent after elective operations, and 16 per cent after emergency surgery; the corresponding mortality rates for Group 2 were 3 per cent, 1 per cent, and 20 per cent. Emergency surgery was associated with a significantly higher incidence of perioperative death at any age ($P < 0{\cdot}001$) *and most deaths resulted from complications of coexisting medical disorders or thrombo-embolic complications. Crude actuarial 5-year survival curves showed an increased death rate in Group 1 after 18 months and a significantly lower 5-year survival* ($P < 0{\cdot}05$) *but the age-corrected survival curves for the two groups were not significantly different, and it was concluded that the prognosis for colorectal cancer in the elderly is not significantly different from that of younger patients.*

Keywords: Colorectal cancer, geriatric

Colorectal cancer is the second most common malignancy in the United Kingdom[1] and an increasing number of elderly patients are presenting with this disease as the size of the geriatric population increases. A recent study from Birmingham has suggested that the disease has an extremely poor prognosis in the elderly, with high rates of emergency presentation and perioperative mortality[2].

Such observations are likely to cause alarm in the south west of England where large numbers of elderly subjects take up residence after retirement; the purpose of the present study was to determine the immediate and long-term prognosis of elderly patients suffering from colorectal cancer.

Patients and methods

Three hundred and six consecutive patients with adenocarcinoma of the colon or rectum admitted to one surgical unit of the Royal Devon and Exeter Hospital (Wonford) between 1979 and 1985 were studied in a retrospective review. For the purpose of the study the patients were divided into two groups: Group 1 included 171 patients who were aged ≥ 70 years on first presentation; Group 2 comprised 135 patients aged < 70 years.

The data collected included the mode of presentation of the patients, the location and Dukes' classification of the tumours, the incidence of radical and palliative operations, the causes of death and 30-day hospital mortality, and the 5-year survival rates of the two groups. All patients were followed up for 5 years or to the end of the study period (June 1987). The patients were seen at intervals of 6 months for the first 2 years and annually thereafter. Crude and age-corrected actuarial survival curves were constructed for the two groups of patients[3–5], and statistical comparisons were made using the log rank test[6]. The χ^2 test was used in the comparison of other clinical variables in the two groups.

Results

Group 1 comprised 89 male and 82 female patients of average age 77 years (range 70–97); Group 2 comprised 69 male and 66 female subjects of average age 59 years (range 22–69).

One hundred and sixty-six patients in Group 1 (97 per cent) and one hundred and thirty-two patients in Group 2 (98 per cent) underwent resection of the primary growth, and there was no significant difference between the two groups with regard to the location and Dukes' classification of the tumours and the incidence of palliative resections (*Table 1*). Thirty-one patients in Group 1 (18 per cent) and fifteen patients in Group 2 (11 per cent) presented as emergencies with large bowel obstruction or perforation of the growth but the difference between the groups is not statistically significant.

The surgical operations were performed by one consultant surgeon and several junior staff of registrar or senior registrar status: 47 (18 per cent) of the elective operations and 37 (80 per cent) of the emergency operations were performed by the junior staff.

Fourteen deaths occurred within 30 days of surgery, an overall mortality rate of 4·6 per cent, and the surgical mortality rates for the two groups are shown in *Table 2*. The total mortality rate for Group 1 (6 per cent) was not significantly higher than that of Group 2 (3 per cent) but emergency operations for obstruction or perforation were associated with a very high surgical mortality in both groups (16 per cent in Group 1 and 20 per cent in Group 2). The 17 per cent total surgical mortality for emergency operations in this study was significantly higher than the 2 per cent mortality rate for elective operations ($\chi^2 = 17{\cdot}06$, $P < 0{\cdot}001$). The causes of death in the 14 patients failing to survive elective or emergency operations are listed in *Table 3*: most patients died of complications of coexisting cardiovascular or respiratory disease or pulmonary embolism rather than complications directly attributable to the surgery.

The crude 5-year actuarial survival curves for the two groups of patients are shown in *Figure 1*. There was little difference between the groups for the first 18 months after surgery but thereafter an increasing death rate was encountered in patients aged 70 years or more on initial presentation (Group 1), and

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Table 1 *Location and Dukes' classification of tumours, and incidence of palliative resections in the two groups of patients*

	Group 1	Group 2
Number of patients	171	135
Location of tumour.		
Rectum	69 (40)	56 (42)
Sigmoid colon	42 (25)	34 (25)
Right and transverse	52 (30)	37 (27)
Descending colon	8 (5)	8 (6)
Dukes classification:		
A	13 (8)	3 (2)
B	72 (43)	59 (45)
C	81 (49)	70 (53)
Nature of surgery·		
Radical resection	118 (69)	95 (70)
Palliative resection	48 (28)	37 (28)
No resection	5 (3)	3 (2)

Figures in parentheses are percentages

Table 2 *Perioperative mortality rates in the two groups of patients*

Postoperative deaths	Group 1 $n=171$	Group 2 $n=135$
Total number	10 (6)	4 (3)
Elective surgery	5 (4)	1 (1)
Emergency surgery	5 (16)	3 (20)

Figures in parentheses are percentages

Table 3 *Causes of perioperative mortality*

Cause of death	No. of patients
Cardiac failure or myocardial infarction	5
Pulmonary embolism	4
Respiratory failure	3
Anastomotic leak	1
Peritoneal sepsis	1*

* Perforated carcinoma of caecum

the 5-year survival rate for this group was significantly lower than that of patients aged less than 70 years (log rank $\chi^2 = 3{\cdot}86$, d.f. $= 1$, $P < 0{\cdot}05$). However, this difference appears to be attributable to an increased mortality from other causes in the elderly, and there was no significant difference in the age-corrected 5-year survival rates for the two groups of patients (*Figure 2*).

Discussion

In a study of 522 patients over 70 years of age presenting with colorectal cancer in Birmingham, Waldron *et al.*[2] suggested that such cases have a bleak prognosis: 58 per cent presented as emergencies with intestinal obstruction or perforation; the perioperative mortality rate was 18 per cent for elective operations and 38 per cent after emergency surgery In a similar study of 150 elderly patients undergoing resections for colonic carcinoma in Copenhagen, Jensen *et al.*[7] encountered an overall surgical mortality of 13 per cent, and emergency operations for intestinal obstruction were associated with a 46 per cent mortality rate. Approximately 50 per cent of the deaths in the latter study resulted from anastomotic dehiscence and other surgical complications.

A significantly lower surgical mortality was encountered in the present study, and the mortality rate in elderly patients did not differ significantly from that of younger patients undergoing resections for colorectal cancer: the overall surgical mortality in patients aged 70 years or more was 6 per cent (the mortality rate for elective surgery was 4 per cent and emergency operations had a 16 per cent mortality rate). The corresponding mortality rates for patients aged less than 70 were 3 per cent, 1 per cent, and 20 per cent. Emergency operations at any age were associated with a significantly higher perioperative mortality, and it might be construed that this reflects unfavourably on the surgeons performing the operations, most of whom were junior staff of registrar or senior registrar status. However, most deaths after emergency surgery resulted from complications of coexisting cardiovascular or respiratory diseases, or thrombo-embolic complications. Similar findings were reported by Boyd *et al.*[8] in a study of 357 patients undergoing colorectal resections, 70 per cent of which were operations for carcinoma. The perioperative mortality in 141 patients aged more than 70 years was 3 per cent in elective operations and 18 per cent after emergency surgery. Most deaths in this study also resulted from complications of coexisting medical disorders irrespective of the age of the patient. Provided that technical mishaps and serious surgical complications are avoided it appears, therefore, that the principal determinants of perioperative mortality in operations

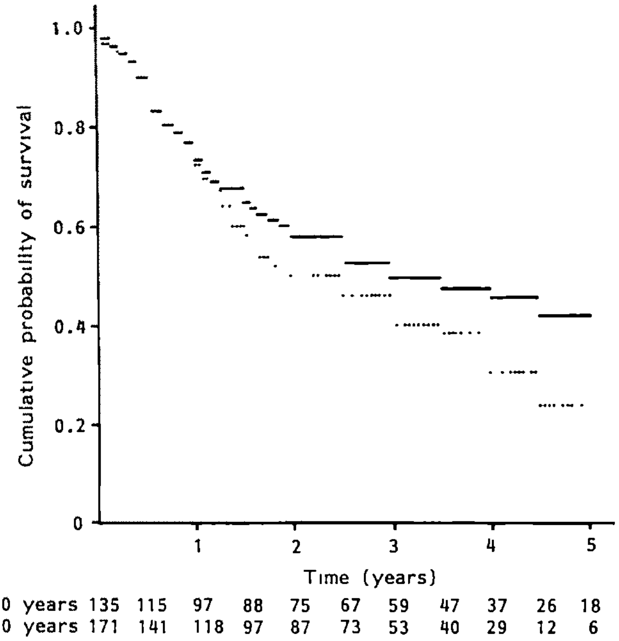

Figure 1 *Crude actuarial 5-year survival of patients aged ≥70 years (· , Group 1) and patients aged <70 years (——, Group 2)*

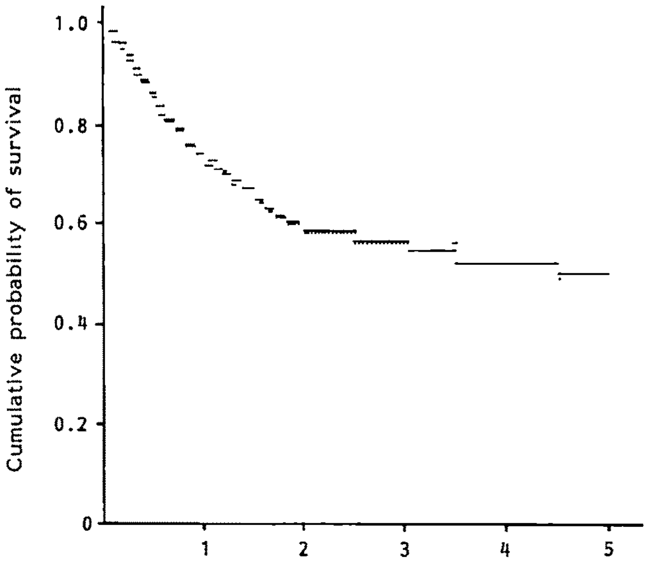

Figure 2 *Age-corrected 5-year survival of patients aged ≥70 years (· · , Group 1) and patients aged <70 years (——, Group 2)*

for colorectal cancer in all age groups are the incidence of emergency operations for intestinal obstruction or perforation and the presence or absence of coexisting medical disorders.

The factors accounting for the relatively low incidence of emergency presentation of colorectal cancer in this study and the unusually high incidence in the Birmingham study[2] are uncertain. Different referral patterns to specialist and non-specialist surgical units undoubtedly influence the proportions of elective and emergency cases, but differences in public awareness and standards of primary care may also influence the mode of presentation.

Previous studies have suggested that the long-term prognosis for colorectal cancer in the elderly is also unfavourable. The 5-year survival rate for elderly patients with operable tumours in Copenhagen was 37 per cent, and this figure compares unfavourably with an expected survival rate of 62 per cent for this age group in population statistics[7]. No long-term survival data were available in the Birmingham study[2] but it was suggested that the pathology of tumours in the elderly may be relatively unfavourable.

The Dukes' classification of the tumours in the present study was similar in elderly and younger patients, and the resection rates and incidence of palliative operations were virtually identical in the two groups. The crude 5-year survival curves showed an increased death rate in elderly patients after 18 months compared with the younger age group, but this might reasonably be attributed to deaths from other causes in a group of patients with an average age of 77 years on initial presentation. The patients in this study were followed up at annual intervals after the first 2 years and most deaths were notified by the general practitioners. On the basis of such information we believe that the excess death rate in the elderly is explained by causes other than the colorectal malignancy, and this conclusion is supported by the finding that the age-corrected 5-year survival curves were virtually identical for the two groups of patients. The probability of survival from colorectal cancer was the same in both groups.

We would conclude, therefore, that age is not a significant prognostic factor in patients presenting with colorectal cancer in the south west of England. Elderly patients have a reduced long-term life expectancy due to deaths from other diseases but the large bowel malignancy can be treated by standard methods of surgical resection with the expectation that the perioperative mortality and probability of cure will not differ significantly from that of younger patients.

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Outcome of patients with rectal cancer treated by stapled anterior resection

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The mortality, morbidity and long-term survival in stapled anterior resection for rectal carcinoma has been analysed in 74 patients. Twelve patients were Dukes' A, 26 B, 29 C, and 7 'D' (submitted to hepatic resection). Operative mortality rate was 3 per cent. Three patients (4 per cent) had clinical anastomotic leakage. Two patients (3 per cent) developed anastomotic stenosis. Local recurrence was present in three patients (4 per cent). The mean (±s.e.m.) overall survival rate at 5 years was 67±6 per cent. There was no significant difference in survival between Dukes' B and C (70±10 per cent versus *59±10 per cent, P=0·209). Patients with absent local spread had a significantly better 5-year survival rate than those with positive local lymph nodes (80±7 per cent* versus *54±9 per cent, P<0·01). The present results confirm the satisfactory use of the EEA® stapler device for colorectal anastomoses in rectal cancer and in patients with resectable liver metastasis.*

Keywords: Rectal carcinoma, anterior resection, EEA stapler, liver metastasis, hepatic resection

Mechanical stapling instruments have enabled the sphincter to be saved in operations for carcinoma of the rectum Reviewing the literature demonstrates that the EEA stapler (Auto Suture, UK) is a useful surgical instrument, but the reported results, with respect to early and late complications, vary considerably[1–22].

The aim of this study was to evaluate the incidence of mortality, morbidity, risk of subsequent local recurrence and long-term results after stapled resection in rectal cancer.

Patients and methods

The records of 74 patients with operable carcinoma of the rectum who were admitted between 1981 and 1984 were reviewed. Patients with unresectable hepatic or extrahepatic localization of the tumour were excluded.

Thirty-four of the patients (46 per cent) were men and 40 (54 per cent) were women, with a mean (±s.e.m.) age of 65·2±10·9 years for men and 63·3±6·7 years for women (*Figure 1*).

The distance from the anal verge to the lower margin of the tumour, as measured by pre-operative rigid rectosigmoidoscopy, is shown in *Table 1* The degree of differentiation, the presence of local involved lymph nodes and Dukes' classification of each patient's tumour was recorded from the pathologist's report (*Table 2*). Local spread was defined as spread of the primary tumour to surrounding fat, mesentery or adjacent organs. No attempt was made to quantify spread; it was recorded merely as present or absent Mechanical preparation before operation was made by magnesium sulphate and mannitol Each patient was given a single dose of clindamycin and metronidazole orally 48 h before operation No patients received radiotherapy. The whole mesorectum was removed and a distal clearance of ⩾2 cm was obtained in all patients. The rectal stump was not washed out during operation, local irrigation with a cancericidal agent was not used in this study. A 'covering' loop colostomy was not performed

Seven patients with liver metastases but without extrahepatic disease were submitted to hepatic resection: three left lobectomies, two right lobectomies and two wedge resections. The follow-up time for surviving patients ranged from 12 to 58 months after operation with a mean of 37·2±13·4 months Survival data, calculated by life-table method, did not consider operative mortality; statistical differences in survival rates were determined by Z test.

Results

Two patients (3 per cent) died within 30 days of surgery. one patient (aged 75 years) after myocardial infarction and one (aged 66 years) after pulmonary insufficiency; this second patient had a simultaneous right hepatic lobectomy. Wound infections were the most frequent complication (*Table 3*). Three patients (4 per cent) developed anastomotic leakage: all had the tumour in the lower third of the rectum. Two of these patients who had faecal discharge through the drain site subsequently settled on conservative measures. The remaining patient was submitted to transverse colostomy; a Gastrografin® enema

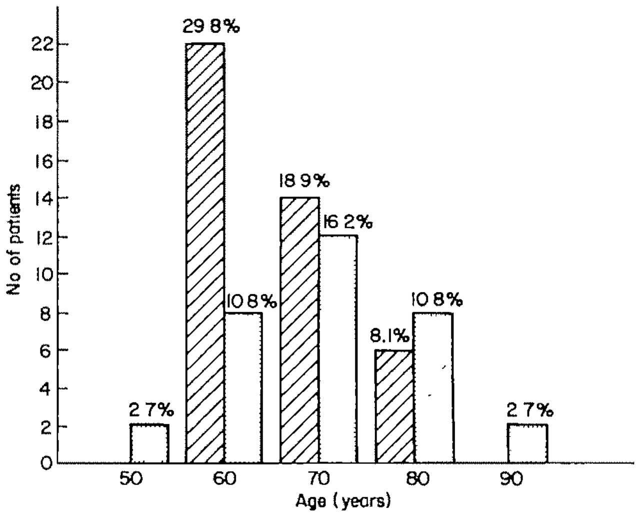

Figure 1 *Age and sex distribution of the 74 patients with carcinoma of the rectum and submitted to colorectal anastomoses with the EEA stapler* ▨, *female,* ☐, *male*

Table 1 *Tumour distance from anal verge*

cm	Number of patients (%)
<6	6 (8)
6–11	26 (35)
11–15	42 (57)

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Table 2 *Tumour details according to Dukes' classification, histological grade of malignancy and the presence of local spread*

Details	Number of patients (%)
Dukes' classification	
A	12 (16)
B	26 (35)
C	29 (40)
'D'	7 (10)
Histological grade	
G 1	40 (54)
G 2	30 (40)
G 3	4 (6)
Local spread	
N −	38 (51)
N +	36 (49)

Table 3 *Postoperative complications*

Complication	Number (%)
Wound infection	5 (7)
Diarrhoea	4 (5)
Temporary incontinence	3 (4)
Anastomotic leakage	3 (4)
Pneumonia	2 (3)

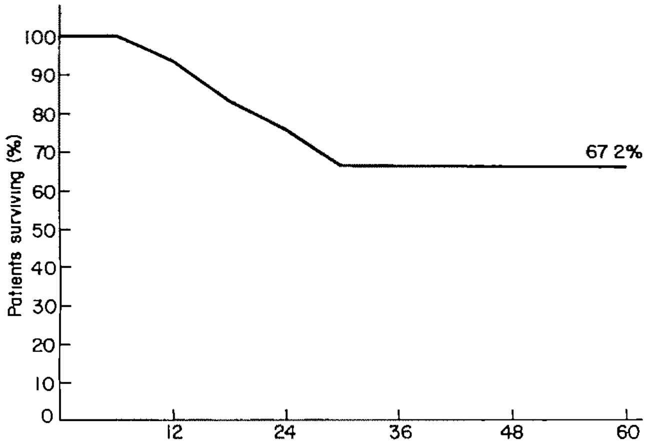

Figure 2 *Overall 5-year survival rate for patients with carcinoma of the rectum who underwent anterior resection*

performed 10 months after surgery showed a satisfactory anastomosis: the colostomy was closed.

Cartridge no. 25 was used in 4 patients, no. 29 in 43 patients and no. 33 in 27 patients.

Two patients (3 per cent) developed anastomotic stenosis 6 and 14 months after operation (in both a no. 29 cartridge was used). The second patient had had postoperative anastomotic leakage. They have responded well to dilatation and biopsies have not shown evidence of recurrent disease.

Three patients (4 per cent) developed local recurrence 6, 7, and 19 months after operation. The first, a Dukes' B case, had a margin of resection of 1·5 cm; the tumour in the lower third of the rectum was submitted to abdominoperineal resection with no recurrence 42 months after the first operation. The second and the third patients, classified as Dukes' C, with a margin of resection of 3 and 5 cm and the tumour in the lower and middle third of the rectum respectively, developed liver metastases and were submitted to transverse colostomy.

The overall mortality curve is shown in *Figure 2* and shows a mean (±s.e.m.) 5-year survival rate of 67±6 per cent.

There was no significant difference in survival when patients with Dukes' B and C carcinoma were compared (70±10 per cent *versus* 59±10 per cent, $P = 0{\cdot}209$) (*Figure 3*). Patients with absent local spread had a significantly better 5-year survival rate than those with positive lymph nodes (80±7 per cent *versus* 54±9 per cent, $P < 0{\cdot}01$) (*Figure 4*). The group of seven patients submitted to hepatic resection had a 33±19 per cent 5-year survival rate (*Figure 3*). One of these patients is still alive 56 months after surgery without known recurrences.

Discussion

There is no doubt that circular stapling devices have enabled a low resection for rectal carcinoma to be performed. Since the Auto Suture EEA instrument was introduced in 1977, numerous reports of the use, results and complications have been published.

The different reported incidence of anastomotic leakage may be due to the experience of the surgeon and the method used for determining the leakage (radiological examination *versus* clinical symptoms)[16]. Despite complete tissue rings, three cases of clinical anastomotic leakage (4 per cent) occurred in the present study: only one patient needed a temporary colostomy, the other two were managed conservatively. Leakage with subsequent inflammatory reaction was certainly the reason for

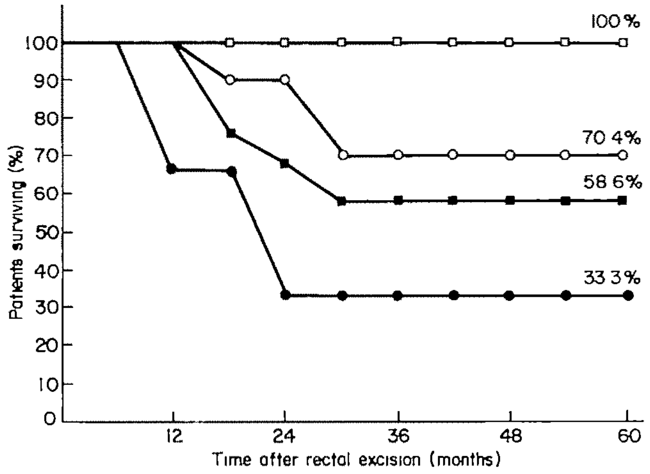

Figure 3 *Five-year survival rates in relation to Dukes' classification* □, *A*, ○, *B*, ■, *C*, ●, *'D'*

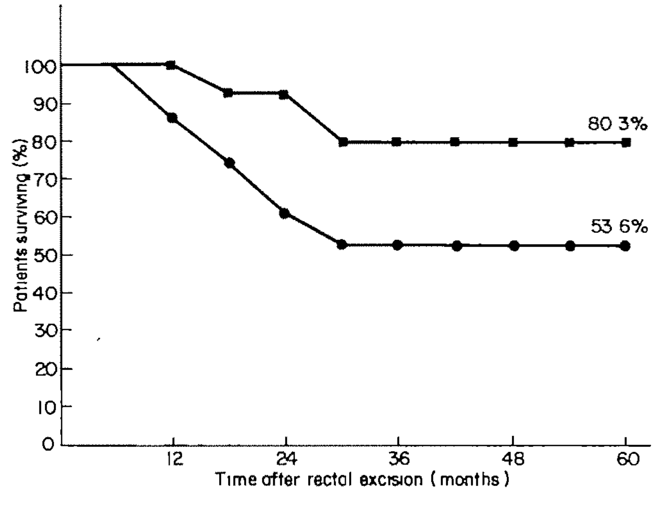

Figure 4 *Five-year survival rates in relation to local spread* ●, *Positive nodes*, ■, *negative nodes*, $P < 0{\cdot}01$

stricture formation in one of these patients. These favourable data strongly confirm the feasibility of avoiding prophylactic diverting colostomy in elective sphincter-saving resection of the rectum using the EEA stapler[5,13].

In our experience only two patients, who had had anastomoses in the lower third of the rectum, developed early postoperative incontinence, which improved spontaneously. These and reported data confirm the low incidence of incontinence after sphinter-saving resection of the rectum[10]. Nevertheless, in the elderly the risk of postoperative incontinence may be increased[4] and we suggest a correct preoperative manometric assessment of sphincter continence.

The problem of local recurrence remains debatable because most studies are retrospective[6,8,9,11,12,14,15,17–21]. Moreover, patients may have silent metastases which cannot be detected by clinical or radiological methods especially after abdominoperineal resection while in sphincter-saving resection the local recurrence is far easier to detect. Selected patients with pelvic recurrence of rectal cancer may be submitted to abdominoperineal or abdominosacral resection without diminishing long-term survival[23].

Our data are too small to compare local recurrence with the Dukes' classification, histological grading, tumour diameter and localization in the rectum. However, according to the literature, patients with a Dukes' C tumour located in the lower third of the rectum are more at risk from local recurrence[6,8,9,11,18,21]. Significant mortality was seen at 5 years in patients with local spread when compared with those without local involved lymph nodes. Recently there has been an increased interest in hepatic resection for synchronous and metachronous colorectal liver metastases. Neither the size of metastases, as long as they could be completely resected, nor the Dukes' classification of primary cancer affected the outcome after resection[24]. Nevertheless only a minority of patients (5–25 per cent) with solitary or unilobar deposits are considered to be candidates for liver resection[24].

In conclusion, our long-term results, incidence of anastomotic leakage and local recurrence in patients with rectal cancer and thus submitted to anterior resection of the rectum confirm the satisfactory use of the EEA stapler device for colorectal anastomoses. The incidence of anastomotic leakage and local recurrence is particularly high when the tumour is in the lower third of the rectum. Patients with rectal cancer and resectable liver metastases may be safely submitted to restorative surgery of the rectum at the same time as hepatic resection.

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CONTENTS IN BRIEF

EDITORIAL OPINION

537 **Scientific Basis of "Aggressive Traumatology" in Lesions of the Locomotor System.** Martin Allgower

SCIENTIFIC PAPERS

540 **The Case for Selective Cholangiography.** Robert O. Gregg

546 **Subclavian-External Carotid Bypass for Symptomatic Severe Cerebral Ischemia From Common and Internal Carotid Artery Occlusion.** Clifford L. McGuiness, Dwight H. Short, and Morris D. Kerstein

551 **Comparison of Transcutaneous Oximetry, Vascular Hemodynamic Measurements, Angiography, and Clinical Findings to Predict the Success of Peripheral Vascular Reconstruction.** Harry B. Kram, Paul L. Appel, and William C. Shoemaker

559 **Hyperglycemic Hyperosmolar Nonketotic Dehydration in Relation to Blood Ketone Body Ratio in Partially Hepatectomized Rabbits.** Toshio Nakatani, Kazuhiro Yasuda, and Kazue Ozawa

564 **Selective Distal Splenorenal Shunt Versus Side-to-Side Portacaval Shunt. Clinical Results of a Prospective, Controlled Study.** Gian P Spina, Fabrizio Galeotti, Enrico Opocher, Roberto Santambrogio, Giovanni Cucchiaro, Carmelo Lopez, and Giuseppe Pezzuoli

572 **Overinflation of Pneumatic Antishock Garments in the Elderly.** John A. Savino, Ihsan Jabbour, Nanakram Agarwal, and Dan Byrne

578 **The Reason for Cardiac Output Reduction After Aortic Cross-Clamping.** Simon Gelman, Holt McDowell, Pamela D. Varner, James Pearson, John Ebert, Gwendolyn Graybar, and James Proctor

587 **Surgical Treatment of Ventricular Septal Rupture Complicating Myocardial Infarction.** Thomas C. Litton, John P. Sutton, Claude W. Smith, William B. Allen, John W. Yarbrough, and Edward M. Leppard

590 **Heart and Kidney Transplantation in the Rat Using a Mixed Cuff-Stent Microsurgical Technique.** Antonio Marni and Maria E. Ferrero

594 **Factors Influencing the Morbidity of Colostomy Closure.** Demetrios Demetriades, Akis Pezikis, John Melissas, Dilipkumar Parekh, and Gordon Pickles

597 **Analysis of Techniques and Results in 347 Consecutive Colon Anastomoses.** Steven A. Curley, David C. Allison, Daniel E. Smith, and Raymond C. Doberneck

602 **Effects of Intermittent Pneumatic Leg Compression for Prevention of Postoperative Deep Venous Thrombosis With Special Reference to Fibrinolytic Activity.** Kiyoshi Inada, Shigefumi Koike, Naoki Shirai, Koji Matsumoto, and Mitsuo Hirose

HOW I DO IT

606 **Retroperitoneal Approach to the Warren Shunt.** Kim J. Hodgson, Dhiraj M. Shah, Robert P. Leather, John D. Corson, and Allastair M. Karmody

611 **Single-Layer End-On Continuous Suture of Colonic Anastomoses.** Felix Harder and Peter Vogelbach

615 **A New Incision for Subfascial Ligation of Perforating Veins in Chronic Venous Ulcers of the Leg.** Nilakantan Ananthakrishnan, Satya Parkash, and Subendra N. Banerjee

616 **Endoscopic Implantation of Iridium Wire for Treatment of Carcinoma of the Bile Duct.** T. Jeffery Wieman and William J. Spanos

SURGICAL PHARMACOLOGY

619 **Oral Contraceptive Agents: Current Status.** Byron J. Masterson

EDITORIAL COMMENT

545 **Selective Operative Cholangiography.** Stanley O. Hoerr

628 **Book Reviews**

629 **Letters to the Editor**

630 ***The British Journal of Surgery* Table of Contents (vol. 75, no. 3, March 1988)**

A34 **Information for Authors**

Br. J. Surg. 1988, Vol. 75, May,
425–427

Rigid sigmoidoscopy: an evaluation of three parameters regarding diagnostic accuracy

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Rigid sigmoidoscopy is the method employed for examining the rectum and sigmoid colon in most general surgical clinics. Commonly, this is performed without any prior preparation of the bowel and with the patient in the left lateral (Sims') position. This study was designed to assess three factors relating to this method: preparation of the bowel; position of the patient; and the experience of the operator. The study shows that diagnostic accuracy without preparation is adequate in only 50 per cent of cases but, by employing a preliminary disposable (Fletcher's) enema, this can be improved to 80 per cent. Employing the knee–elbow position gave only slight advantage over the usual Sims' position and operator experience did not improve diagnostic accuracy once familiarity with the use of the sigmoidoscope had been achieved. The study underlines the importance of preparation as an essential prelude to sigmoidoscopy.

Keywords: Rigid sigmoidoscopy, diagnostic accuracy, preparation

Rigid sigmoidoscopy is carried out to identify pathology in the rectum and lower sigmoid colon, up to 25 cm from the anal verge. Although flexible sigmoidoscopy and colonoscopy are being more widely used, rigid sigmoidoscopy is still the most common initial diagnostic outpatient procedure in this area. In most surgical clinics, patients with symptoms suggestive of colorectal pathology are assumed to be disease-free when both rigid sigmoidoscopy and barium enema have been reported as showing no abnormalities. As most surgeons will continue to rely on rigid sigmoidoscopy for office diagnostic purposes in the rectum and rectosigmoid zone, it is important that it is carried out by the most accurate method. At St. Mark's Hospital the standard method for sigmoidoscopy employed in the outpatient department is for the examination to be performed in the left lateral (Sims') position without any bowel preparation. This study was designed to assess the following factors relating to this standard method: the unprepared bowel *versus* the prepared bowel; the left lateral position *versus* the knee–elbow position; and the experience of the operator.

Patients and methods

The study was conducted, over a period of 3 months, in the outpatient department of St. Mark's Hospital. The three operators were a consultant (C.V.M.), a senior registrar (P.G.), and a registrar (P.B.F.). All patients undergoing sigmoidoscopy during the study period in the clinic were included. The patients ranged from 19 to 87 years and the range of colorectal disorders represented was wide (*Table 1*). More specifically, as regards case mix, 49 per cent of patients attended for various anal disorders (mainly haemorrhoids), 14 per cent for neoplasms (mainly follow-ups), 14 per cent suffered from inflammatory bowel disease, 6 per cent were labelled as cases of irritable bowel syndrome and 4 per cent as simply 'constipated'. Two-thirds of the patients had undergone sigmoidoscopy before.

The unprepared bowel

For this part of the study patients were randomly allocated into two groups: group A with no preliminary bowel preparation and group B with a preliminary disposable phosphate (Fletcher's) enema, given immediately before the examination. The patients were allowed to evacuate the enema completely before undergoing sigmoidoscopy. Both groups were sigmoidoscoped in the standard left lateral (Sims') position[1], the patients being positioned with the buttocks over the edge of the examining couch and elevated by a sandbag under the left hip, with the trunk being angled across the couch away from the operator, and both hips and knees flexed. The smaller Lloyd-Davies rigid sigmoidoscope (25 cm long and 13 mm in diameter) was used for each case and the operator recorded the distance to which the sigmoidoscope could be passed and the clarity of the view which was subjectively assessed as good, fair or poor. A good view was defined as an examination which allowed a perfect view, such that no pathology could have been overlooked; a fair view was defined as an examination in which faecal contamination was present, but where major pathology (e.g. a polyp > 1 cm in diameter) would not have been missed; a poor view was where sufficient faecal material was present to prevent a proper diagnostic appraisal. At the conclusion of the first part of the study there were 100 patients in group A and 90 patients in group B, and each operator had performed approximately one-third of the examinations in each group.

The left lateral position

In this part of the study, a group of 25 new outpatients (group D) were sigmoidoscoped in the knee–elbow (or jack-knife) position, after

Table 1 *Final diagnoses*

Final diagnosis	*n*
Minor anal conditions	105 (49)
Haemorrhoids	73
Mucosal prolapse	13
Fissure-in-ano	8
Pruritis ani	8
Fistula-in-ano	3
Functional bowel disorders	36 (17)
Irritable bowel syndrome	13
Perineal pain syndromes	9
Constipation	8
Diverticulosis coli	4
Incontinence	2
Inflammatory bowel disease	31 (14)
Neoplastic diseases	30 (14)
Miscellaneous/undecided	13 (6)
Total	215

Values in parentheses are percentages

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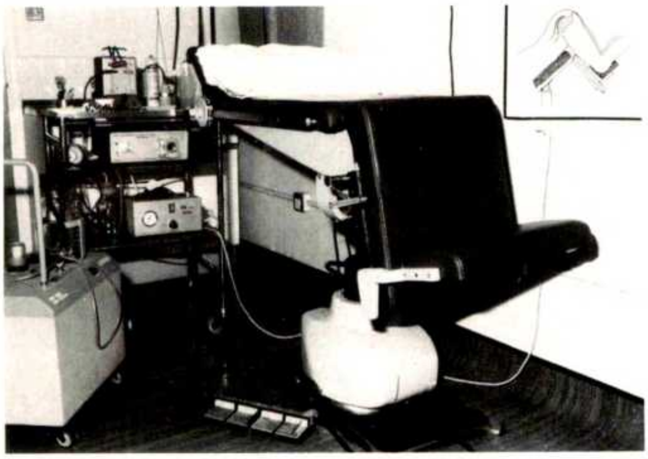

Figure 1 *The Ritter table*

Table 2 *Distances achieved*

	Area examined			
	Rectum only	Rectum + recto-sigmoid junction	Rectum + lower sigmoid	Mean distance (cm)
Distance from anal verge (cm)	0–15	16–24	25	—
Group A (no preparation) $n=100$	34 (34)	45 (45)	21 (21)	19·3
Group B (enema) $n=90$	18 (20)	36 (40)	36 (40)	20·7
Group C (enema + Sims' (position $n=30$	2 (6)	14 (47)	14 (47)	22·0
Group D (enema + knee–elbow position) $n=25$	2 (8)	9 (36)	14 (56)	22·4

Values in parentheses are percentages

preparation of the bowel with a phosphate enema, using the Ritter table (*Figure 1*). The same type of Lloyd-Davies sigmoidoscope was used, and the same criteria as to the distance and quality of the visual appraisal. This group was examined by the consultant and the results compared with those patients in group B, who had been examined by the (same) consultant in the Sims' position (30 cases, group C).

The experience of the operator

For each sigmoidoscopic examination, the name of the operator was recorded. Subsequent analysis of the results regarding distance achieved and view obtained by the consultant, senior registrar and registrar were compared.

Analysis of diagnostic value

A '*complete*' sigmoidoscopy was defined, for the purpose of this analysis, as one in which the instrument was passed to 25 cm and the view was good. A 'satisfactory' sigmoidoscopy was defined as one in which it was considered that no major pathology in the rectum and lower sigmoid colon was missed, the instrument being passed to at least 20 cm and the view being fair or good. Satisfactory, as well as complete, sigmoidoscopies were said to be 'clinically safe'. An 'unsatisfactory' examination was one in which major pathology in the rectum and lower sigmoid colon could have been missed, either as a result of insufficient depth of penetration (< 20 cm) or because of a poor view or a combination of both. An unsatisfactory examination was regarded as being clinically unsafe in that either the instrument had not been passed through the rectosigmoid junction or because a potentially dangerous lesion (e.g. a polyp > 1 cm in size) could have been missed even when a good penetration distance had been achieved.

Results

The unprepared bowel versus *prepared bowel*

The results showed that in both groups A and B (*Table 2*) the levels to which the instrument was introduced were similar, the means being 19·3 cm for group A (no preparation) and 20·7 cm for group B (enema). In both groups there were large numbers of patients (34 per cent in group A and 20 per cent in group B) in whom the instrument did not go through the rectosigmoid junction, i.e. beyond 15 cm. The major benefit from giving bowel preparation lay in giving a greatly improved view; this was shown by the fact that in group A good views were recorded for 52 per cent of patients, while in group B a good view was achieved in 87 per cent (*Table 3*).

When distance and clarity were combined for analysis (*Table 4*) the results were weighted heavily in favour of preparation.

The left lateral position versus *the knee–elbow position*

As far as the position for sigmoidoscopy is concerned, the mean distance achieved by the consultant for group C (Sims' position)

Table 3 *Clarity of view*

	Visual appraisal			Major pathology not missed (%)*
	Poor	Fair	Good	
Group A (no preparation) $n=100$	21 (21)	27 (27)	52 (52)	79
Group B (enema) $n=90$	4 (4)	8 (9)	78 (87)	96
Group C (enema + Sims' (position) $n=30$	2 (7)	1 (3)	27 (90)	93
Group D (enema + knee–elbow position) $n=25$	1 (4)	0	24 (96)	96

Values in parentheses are percentages. * These figures are obtained by adding fair and good percentages

Table 4 *Diagnostic accuracy*

	Assessment			
	Unsatisfactory	Satisfactory	Complete	Clinically safe (%)*
Group A (no preparation) $n=100$	50 (50)	36 (36)	14 (14)	50
Group B (enema) $n=90$	29 (32)	27 (30)	34 (38)	68
Group C (enema + Sims' position) $n=30$	6 (20)	11 (37)	13 (43)	80
Group D (enema + knee–elbow position) $n=25$	5 (20)	7 (28)	13 (52)	80

Values in parentheses are percentages. * These figures are obtained by adding satisfactory and complete percentages was 22·0 cm; compared with the mean of 22.4 cm for group D (knee–elbow position), as shown in *Table 2*. The percentage of complete examinations (*Table 4*) was greater for group D (52 per cent as against 43 per cent for group C) but there still remained a group of five patients in whom the sigmoidoscopy was unsatisfactory. So, for both these groups, the examination was clinically unsafe in 20 per cent of cases.

The experience of the operator

As far as this parameter is concerned, when the results were compared for each of the operators there were no significant differences in the mean distance achieved. Experience does not seem to be as important a factor as preparation and position once good familiarity with the use of a sigmoidoscope has been established.

Discussion

The value of a properly performed sigmoidoscopy is beyond dispute. Colorectal neoplasms commonly occur in the rectum and sigmoid colon[2], and the procedure has long been regarded as an essential preliminary to barium enema for the diagnosis of these lesions. Rigid sigmoidoscopy is a procedure frequently performed, but there is no agreement about the optimum way to carry out the examination and the authors were unable to find data comparing different methods. It has been shown that the instrument is often not passed as far as one thinks[3] and that the region of the rectosigmoid junction is where a lesion may well be missed[4,5]. This same area can also pose problems for the radiologist[4]. Although it has been said that flexible sigmoidoscopy provides the solution to the problem[4–6] and that it is quick and easy to perform[7], the fact remains that most surgeons still rely on rigid sigmoidoscopy for their preliminary appraisal. In most surgical clinics rigid sigmoidoscopy is performed without preparation of the rectum. Some surgeons believe that essential information may be lost after preparation (e.g. the presence of blood, mucus or parasites) or that the enema may so inflame the rectal mucosa as to result in a false diagnosis of inflammatory bowel disease or that it may cause the disappearance of the subtle changes of a mild proctitis.

The authors felt that these arguments were valid only if examination of the unprepared rectum had achieved its main objective, i.e. to pick up major pathology of the rectal mucosa and lower sigmoid colon to a distance of 25 cm from the anal verge. The instrument should at least pass the rectosigmoid junction. The results of this study show that administration of the enema improves the operator's chance of performing a complete sigmoidoscopy, once reasonable familiarity with the use of the instrument has been obtained; however, in clinics where inexperienced doctors (e.g. senior house officer grade) were employed this factor might be relevant, and would make the need for optimum conditions even more important. In such situations, it would seem that the use of bowel preparation and the knee–elbow position would be imperative. In this study, the best conditions for the knee–elbow position were obtained by the use of a Ritter table[8] but this is not essential.

Although objections to the use of bowel preparation have been referred to, it was not found to be disadvantageous in the study. The phosphate enema did not cause significant oedema or reddening of the rectal mucosa; sometimes excess mucus was noted in response to the enema which, in rare instances, required removal by swabs or by suction. However, flexible sigmoidoscopy also requires preliminary preparation, so there is no advantage to be gained by preferring fibreoptic methods in this regard. The study showed that unless the lower bowel is prepared (in this case, by a Fletcher's enema) the chances of an incomplete examination, even in expert hands, were as high as 50 per cent. The information obtained by the study has emphasized the need for preliminary preparation of the rectum and lower colon for satisfactory sigmoidoscopic examination. In the presence of a prepared rectum and sigmoid colon, diagnostically satisfactory examinations can be achieved in 80 per cent of cases.

Preparation in this study took the form of a preliminary enema. This did not seem to cause problems for the running of the clinic, but probably the situation would be more difficult in less well-equipped district hospitals. Alternative methods of preparations (e.g. bisacodyl or Picolax, Nordic Pharmaceuticals Ltd., UK) to empty the lower bowel might be necessary to ease problems associated with using enemas on large numbers of patients in a busy general surgical clinic. However, in so far as the results obtained at a specialist colorectal institution (St. Mark's) for a standard method of sigmoidoscopy (unprepared bowel, Sims' position) show that the examination is diagnostically secure in only 50 per cent of cases, the need for an improvement is self-evident. Otherwise, examples of missed cancers of the rectum and lower sigmoid colon will continue to occur.

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Cerebral angiography for cerebrovascular disease: the risks

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Cerebral angiography is still suggested as a first line investigation for patients with putative transient ischaemic attacks (TIA) and it is considered by most surgeons as a necessary prelude to carotid endarterectomy. That conventional cerebral angiography involves risk is well known, although the magnitude of this risk is not. Prospective studies of cerebral complications from this technique, published over the last decade, have been analysed to show that the major stroke rate after conventional cerebral angiography for patients with TIAs is likely to be about 2·4 per cent. This must be taken into account if the true morbidity of carotid endarterectomy is to be appreciated (assuming conventional angiograms have been used). Furthermore, since many sufferers are assessed by angiography but not submitted to surgery, a policy of conventional angiography for patients with TIAs puts a far greater number at risk than that actually having carotid endarterectomy.

Keywords: Cerebral angiography, carotid angiography, carotid endarterectomy, transient ischaemic attack

An estimated 130 000 to 135 000 carotid endarterectomies were performed in the USA in 1986[1] and 1500 were carried out in the UK. The risk of operation varies widely with reported perioperative stroke and/or death rates of between 1 per cent and 21 per cent[2]. a rate of ≤3 per cent has been mooted as acceptable for prophylactic carotid surgery[3,4]. It has been suggested that patients with transient ischaemic attacks (TIA) should be investigated by angiography without recourse to non-invasive tests[5,6], and it is certainly the case that the vast majority of surgeons in the UK require conventional angiograms before undertaking carotid endarterectomy[7]. While the inherent risk of conventional angiography is well known, the magnitude of contemporary risk from this technique is less well appreciated. Studies of cerebral complications from angiography carried out in patients with TIA or stroke between 1957 and 1977 describe rates which vary from 0 to 28 per cent[8]. Furthermore, data from the UK–TIA Aspirin Trial showed that of 304 patients who had angiography, only 41 eventually had carotid surgery[9], which implied that for each carotid endarterectomy performed 7·4 angiograms were carried out.

The various risks of carotid endarterectomy quoted in the literature naturally refer to the selected subset of patients which actually has the operation. Very rarely does the literature account for the risk of pre-operative angiography and never does it account for the incidence of complications in those patients who have angiography but no operation. The aim of the present study is to review the available prospective data on the cerebral complications of conventional angiography for TIA and so arrive at a realistic estimation of the wider 'pre-operative' risk of pursuing a policy of carotid endarterectomy for symptomatic carotid artery disease.

Definition of cerebral complications

Uniformity of definition and classification is a prerequisite for any useful comparison of data from different studies. Such uniformity is often lacking in the literature dealing with cerebral complications following cerebral angiography. Some early studies contain data only on patients with post-investigation 'stroke'[10–13], while others do not differentiate between stroke and TIA[14–20]. A TIA may be defined as an acute episode of focal neurological or ocular symptoms lasting <24 h and thought to be due to vascular disease of an arterial embolic or thrombotic nature. Minor stroke may be defined in an analogous fashion but with symptoms for up to 1 week. Major stroke lasts for more than 1 week. These definitions are similar to those proposed by the *ad hoc* Committee for the Classification of Cerebrovascular Disease[21] and they are used in the present article for evaluating available data.

Incidence of cerebral complications

It is important to have detailed pre-angiographic information on the neurological status of patients to appreciate the relationship of any change in such status to angiography. Any neurological deterioration within 24 h of angiography should be included as a neurological complication. Therefore, we agree with Earnest *et al.*[22] that the following conditions are necessary for accurate analysis of complication rates: prospective accumulation of data; neurological examination before and after angiography, and the inclusion of all complications, especially all neurological events that occur during or soon after angiography.

To make our evaluation as contemporary as possible we have examined the literature during the last 10 years. Between 1977 and 1987 only five prospective studies were located which satisfy most of the above conditions[8,22–25]. Although a further large prospective study of 3730 patients exists, the data do not include a breakdown of the group profile of patients undergoing angiography, making it impossible to deduce the complication rate in that group of patients with cerebrovascular disease[26]. Even in the five prospective studies which satisfy most of our criteria, the lack of uniformity of definition of neurological complications complicates the analysis

Mani *et al*[27] combined the criteria of Wishart[15] and Takahashi and Kawanami[20] and they use the terms 'transient' and 'permanent' to describe complications which persisted for ≤10 days and >10 days, respectively. This study of 1296 cases reports no 'permanent' neurological complications 'Transient' complications occurred in 12 of 1013 cases (1·2 per cent) in non-training hospitals and in 12 of 283 cases (4·2 per cent) in training hospitals, giving an overall value of 24 of 1296 cases (1·9 per cent). However, using our more conventional definitions, these figures would almost certainly contain patients who would be classified as having sustained a stroke from angiography. Unfortunately no numerical value can be placed

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Table 1 *Complication rates after cerebral angiography for cerebrovascular disease*

Author	Year	Number of patients	Complications (%) TIA	Minor stroke	Major stroke
Faught *et al.*[8]	1979	147	6·8*		5·4
Earnest *et al*[22]	1983	637	3·4	0·2	0·6
Skalpe and Ankle[24]	1983	42*	4·8	0	2·4
McIvor *et al.*[25]	1987	230	3·0	2·6	5·6

TIA, transient ischaemic attack; * See text

on this and so the study has been excluded from the remainder of the analysis.

Of 100 patients studied by Skalpe and Ankle[24], 42 had arteriosclerotic disease on radiological assessment. Three neurological complications occurred, two TIAs and one major stroke, and in every case the history suggested a clinical diagnosis of cerebrovascular disease. It must be noted, however, that the group profile of patients investigated here was constructed according to angiographic appearance and the group in which the three complications occurred was not clearly stated.

Although Faught *et al.*[8] are not totally specific in their classification of 'transient' and 'persistent' cerebral complications, it is certain that in the 'persistent' group the complications were still present at the time of discharge from hospital. It does not seem unreasonable, therefore, to assume that these were major strokes, with an incidence of 5·4 per cent. A rate of 6·8 per cent was recorded in the 'transient' group which would presumably include both TIA and minor stroke. This report, along with those of Earnest *et al.*[22] and McIvor *et al.*[25], form the three prospective studies which undoubtedly provide the most comprehensive information, and the relevant data (along with that from Skalpe and Ankle[24]) are summarized in *Table 1*. Combining all available data from the four studies in *Table 1* yields a mean major stroke rate after cerebral angiography of 2·4 per cent.

Discussion

In the light of the above information it would seem reasonable to add an extra 2·4 per cent for angiographic hazard to most of the various figures published on the perioperative stroke rate for carotid endarterectomy and it would be useful for doctors to be aware not only of the perioperative stroke rate in their own institution but also of the periangiographic stroke rate. It is known that the risk of angiography varies from centre to centre and depends not only on the age and general vascular state of the patient but also on the radiological facilities and skills available locally[28]. Furthermore, it has been suggested that cerebral angiography should be performed only in centres with neurological and neuroradiological skills, although even there the risk of permanent neurological impairment is likely to be between 0·2 and 5·3 per cent[28]

A serious challenge also exists to any investigative policy for patients with possible TIA which includes cerebral angiography as the initial investigation[5,6] as it is probable that the number of patients having angiography will be several times the number going on to have surgery. Those who do not proceed to carotid endarterectomy rarely benefit from cerebral angiography and if an extrapolation is made from the UK–TIA Aspirin Trial figures[9] then, in order to generate a 100 patient group suitable for surgery, 740 cerebral angiograms may be carried out with a 2·4 per cent major stroke complication rate. In other words 18 major strokes may result in an attempt to find 100 candidates for carotid surgery.

Fortunately much can be done to alleviate this situation We can take a careful clinical history. The occurrence of retinal symptoms[29] and brief duration of attacks of transient symptoms[30,31] have been claimed as especially likely to be associated with significant extracranial carotid artery disease. Some authors feel that the presence of a carotid bruit is a further indicator[29,32]. A retrospective study[33] of 139 cases of carotid territory TIAs has shown that carotid stenosis occurred in 47 per cent of patients whose symptomatic involvement was restricted to an arm or a leg or dysphasia, whereas attacks of hemiparesis affecting face, arm and leg or arm and leg were only associated with such disease in 16 per cent of patients. It has also been suggested that only 25 to 29 per cent of patients with TIAs, minor stroke or recovered stroke have significant disease in the extracranial internal carotid artery, whereas 65 per cent of those with amaurosis fugax and 86 per cent of those with both cerebral and ocular symptoms have significant disease in this vessel[34].

A modified plan of investigation for symptomatic patients is of even greater importance. It has been reported from one institution that a battery of non-invasive tests, including oculoplethysmography, periorbital directional Doppler sonography and direct ultrasonic imaging of the carotid bifurcation, has resulted in the proportion of angiographic examinations revealing <49 per cent stenosis of the carotid artery decreasing from 49 per cent in 1978 to 19 per cent in 1983. In the same period the proportion of angiographic examinations identifying 75 to 99 per cent stenosis increased from 20 per cent to 62 per cent[35]. Many authors have established high levels of accuracy for a variety of non-invasive methods of evaluating carotid artery disease[36–40]. In the UK various forms of Doppler ultrasonography, particularly Duplex scanning, are popular but these techniques are, sadly, not available to all[41].

It may also be that the neurological hazard of angiography is itself changing with the wider availability of digital subtraction angiography (DSA)[42], although the assumed extra safety of this technique is doubtful especially when the intra-arterial route is chosen for the injection of contrast medium[43]. Intravenous DSA may be safer but only about 80 per cent of studies are likely to be interpretable and because of this it is usually regarded as a screening tool while conventional angiography continues to be advocated before surgery and, indeed, for any patient with hemispheric cerebral symptoms[6,44]. Even those who operate on the basis of intravenous DSA generally demand complete agreement between this test and Duplex scanning[45]. While DSA, by whatever route, may reduce the hazard of conventional angiography, it is not itself free from complications. The technique, however, has an apparent safety which may lead to a lowering of the clinical threshold for cerebral angiography with increased numbers of digital subtraction angiograms being performed as a result. It is conceivable that this new technology may be safer for the individual but not for the community.

It would seem that the sensible investigation of patients with putative transient cerebral ischaemia should always commence with careful clinical evaluation and carotid ultrasonography. Only those with a positive or equivocal result should proceed to angiography (the nature of which should be decided by the surgeon who will be responsible for the carotid endarterectomy, if indicated). If clinical assessment and ultrasonography are omitted then excessive angiography must be the result. The true hazard of carotid endarterectomy then will start well before the time of surgery and will encompass a population far greater than that which eventually has the operation.

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Results of excision of a cervical rib in patients with the thoracic outlet syndrome

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Excision of a cervical rib in patients with the thoracic outlet syndrome has been the subject of debate. One surgeon's experience of 23 cervical rib excisions is presented. Ten operations produced a complete cure, eleven improvement, and two no change in the patient's condition. Of 15 cases with neurological symptoms alone, 9 were cured, 5 improved and 1 was not helped; in contrast, of 8 patients with vascular symptoms, 1 was cured, 6 were improved and 1 was not helped. We conclude that cervical rib resection is the correct treatment for patients whose symptoms are predominantly neurological. Rib resection alone may not be sufficient in patients with vascular symptoms. The management of a cervical rib with vascular involvement is discussed.

Keywords: Thoracic outlet syndrome, cervical rib

Symptoms resulting from compression of the neurovascular bundle at the thoracic outlet have been recognized since the last century. In 1861, at St. Bartholomew's Hospital, the first recorded surgical decompression was performed by Holmes Coote, who successfully removed a large palpable cervical rib[1]. The role of surgical intervention in patients with the thoracic outlet syndrome has been the subject of debate[2], the question being: 'Is resection of a cervical rib a worthwhile procedure when found in conjunction with these symptoms?'

This paper describes our experience of 23 cervical rib excisions in 18 patients.

Patients and methods

Methods

The patients underwent excision of a cervical rib between 1975 and 1986, on the Vascular Surgery Unit at the University Hospital of South Manchester. All were under the care of one surgeon. Their hospital records were studied, X-rays reviewed and additional follow-up information was obtained from a questionnaire.

A supraclavicular approach was used in all cases. After exposing the rib, the anterior end was disconnected from the first rib using an osteotome. It was then freed of muscle attachments as far posteriorly as possible, before being excised with bone-cutting forceps. This approach provided adequate exposure for any vascular reconstruction that was required.

Patients were followed up between 3 months and 9 years.

Patients

Fifteen patients were women (average age 35) and three men (average age 37). Patients were referred from a variety of sources indicating the diversity of presenting symptoms. Only five were referred directly to the vascular unit by their general practitioner. The remainder were sent from other hospital specialists five from orthopaedic surgeons; four from general surgeons; one from a cardiothoracic unit and three from general physicians.

Symptoms had been present between 3 months and 12 years. Pain was dominant in 19, occurring in the hand, forearm, shoulder or neck (*Figure 1*). It was commonly exacerbated by exercise, e.g. carrying heavy shopping and racket sports.

Paraesthesia was the next most common symptom. This was usually confined to the ulnar border of the hand and forearm. Muscle weakness was a less common complaint. Only one patient had symptoms in the distribution of the median nerve.

Coldness, colour changes and/or Raynaud's phenomenon were described in eight patients.

Cervical ribs were palpable in 15 patients (*Figure 2*). Most abnormal signs tended to be in patients with vascular symptoms. Five had weak or absent pulses in the neutral position, and a different set of five had a bruit in the supraclavicular area. One presented with a pulsatile swelling in the neck, and one with severe ischaemic changes in the fingers.

Neurological signs were relatively unusual. No patients had demonstrable sensory abnormalities. Even though nine described muscle weakness, only four had obvious wasting, and this was confined to the small muscles of the hand.

Plain X-rays of the chest, thoracic inlet and cervical spine were diagnostic of the cervical rib in all cases. These demonstrated 12 of the patients to have cervical ribs on both sides, although only 5 patients had bilateral symptoms requiring bilateral excisions.

Arteriograms were not performed routinely, but were reserved for patients with clinical evidence of severe vascular disease. In one patient, they were performed to establish the cause of a pulsatile swelling in the neck, and in a second patient to investigate the cause of severe vascular symptoms and absent pulses.

Nerve conduction studies were performed in four patients to eliminate more distal entrapment neuropathies, such as the carpal tunnel syndrome.

At operation, 18 complete and 5 incomplete ribs were excised. We have defined a complete rib as one which forms a bony or cartilaginous union with the first rib; an incomplete one as a bony projection from the transverse process of the seventh cervical vertebra which does not

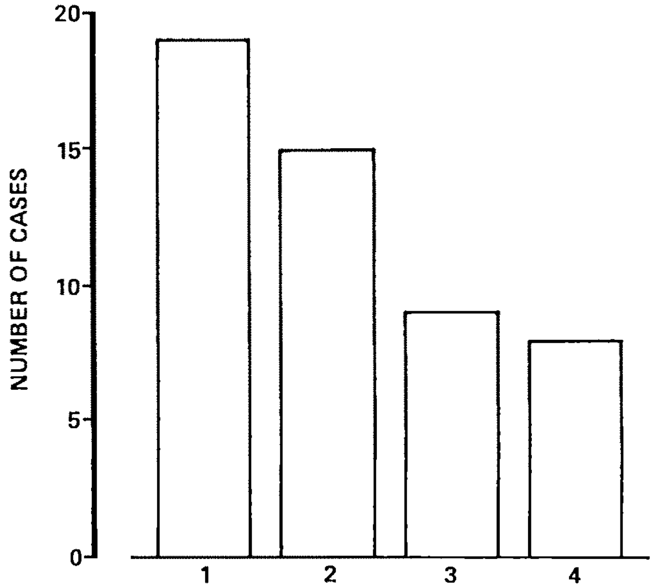

Figure 1 *Distribution of symptoms in 18 patients (5 bilateral cases) referred to the vascular unit*

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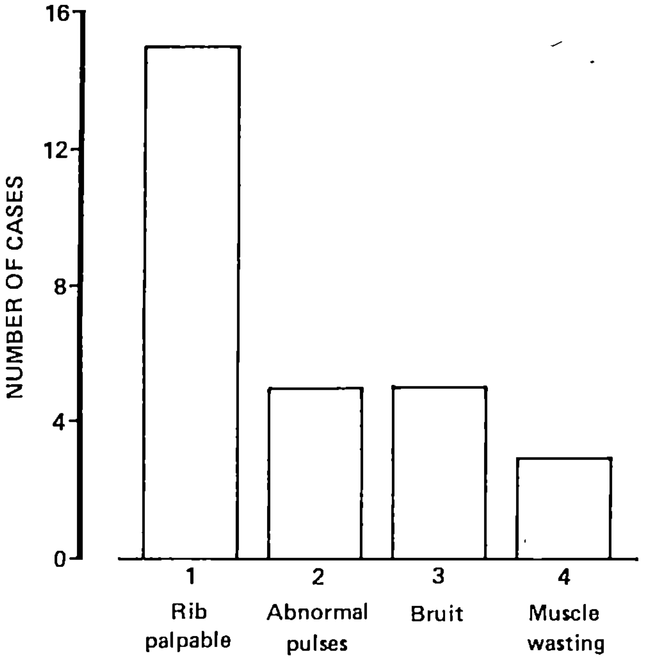

Figure 2 *Distribution of signs in 18 patients (5 bilateral cases) who underwent excision of a cervical rib*

articulate with the first rib, but may be connected to it by means of a fibrous band.

There were no deaths and no major postoperative complications.

In most cases, the rib was found to impinge on the lower roots of the brachial plexus. In five patients there was obvious compression of the subclavian artery Within this group, one aneurysm was found which required resection; one artery was dilated distal to the lateral border of the first rib and another had become completely thrombosed. Vascular involvement was only found in association with complete cervical ribs.

Results

A Visick grade was used initially for assessing the patients' response to treatment, but was later found to be too cumbersome. The results fell naturally into three clear categories. Of the 23 operations, 10 produced a complete cure, 11 improvement, and only 2 patients were not helped by surgery

The extra rib may impinge on either the subclavian vessels or the brachial plexus, so the patients' symptoms were divided into neurological and vascular. Patients with purely neurological symptoms could be identified with some confidence. However, when vascular symptoms were present, it was difficult to decide whether neurological symptoms were also part of the clinical picture. Patients were divided therefore into those with purely neurological symptoms and those in whom vascular symptoms were present, with or without neurological ones.

A complete recovery was much more common in patients with neurological rather than mixed symptoms (*Figure 3a* and *b*). Nine patients with neurological symptoms were cured, five improved, and only one experienced no benefit. Although most patients with vascular symptoms claimed some improvement, only one of the eight experienced complete relief and one received no benefit at all.

The two patients who were not helped by their operation warrant further comment. The first, a woman aged 53, had experienced severe pain, paraesthesia and weakness in her left arm for 12 years. Her condition had deteriorated for a short time before presentation. On examination she was found to have large palpable cervical ribs, marked wasting of the small muscles of the hand and reduced pain sensation in the distribution of the ulnar nerve. There were no vascular signs. Plain radiology, in addition to demonstrating the cervical ribs, showed advanced spondolytic changes in the cervical spine at C_5/C_6 and at C_6/C_7 levels. Electromyographic studies demonstrated widespread abnormalities of sensory nerve conduction consistent with a peripheral neuropathy. Evidence was also found of a degenerative lower motor neurone lesion involving muscles of the left hand, without motor nerve conduction slowing, suggesting a lesion involving T_1 at root or cord level. At operation, the thoracic outlet was amply decompressed by removal of the large extra rib on the left side. At follow-up, no improvement was noted of what was clearly a long-standing and advanced neuropathy.

The second patient was a man of 43 years who presented with a 6-month history of unilateral Raynaud's phenomenon. On examination he was found to have trophic changes at the finger tips and weakened pulses on the affected side. At operation, the subclavian artery was found to be compressed by a complete cervical rib. The rib was excised and a cervical sympathectomy performed in addition. There was some initial improvement, but the arm became pulseless at a later date requiring an emergency brachial embolectomy. It was apparent that this man had suffered severe intimal damage to the subclavian artery, not diagnosed initially, with resulting thrombosis and distal embolic disease.

Discussion

Describing the first surgical removal of a cervical rib; Holmes Coote entitled his article[1] 'Exostosis of the left transverse process of the seventh cervical vertebra surrounded by blood vessels and, nerves: successful removal'. This is an apt description of the complexity of the relations of a cervical rib, and explains the diversity of symptoms it may cause. Shortly after this paper appeared, Gruber, in 1869, published an anatomical study of cervical ribs and devised a classification according to their degree of development[3]. In Manchester,

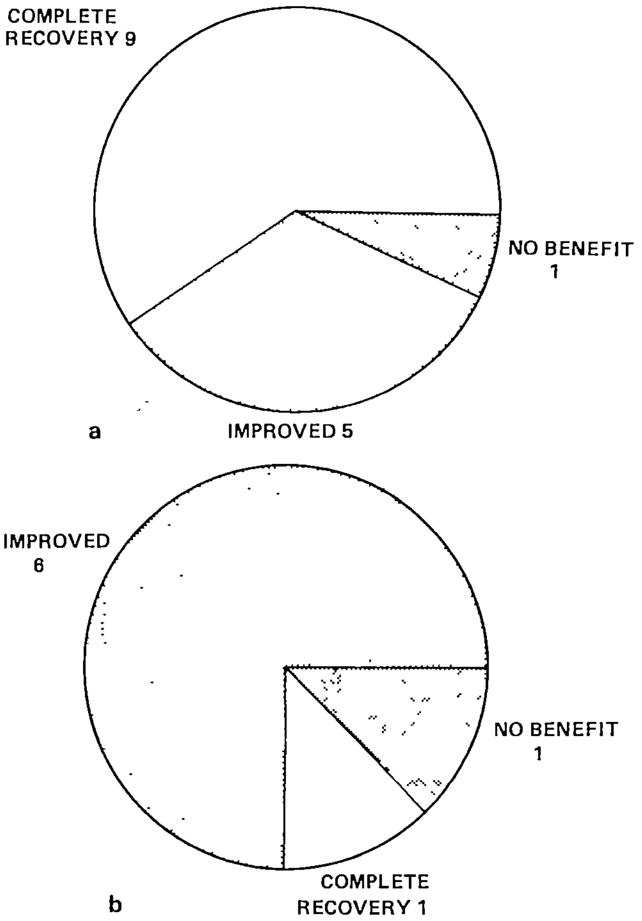

Figure 3 *Results according to symptoms* **a** *patients with only neurological symptoms;* **b** *patients with vascular symptoms with or without neurological symptoms*

Thorburn wrote a treatise on the symptoms produced by cervical ribs in 1907[4]. In 1917, Halstead reviewed 716 cases in the world literature, made a study of the subclavian artery dilatation reported in 27 of them, and conducted experiments to establish the cause[5]. Symonds in 1927 was the first to recognize thrombo-embolic phenomena associated with cervical ribs[6].

Cervical ribs are present in from 0.5 per cent to 1 per cent of the population and are bilateral in > 50 per cent of cases[7,8]. They may vary between a complete rib resembling the first thoracic rib to an exostosis of the transverse process of C_7. As reflected in our series, cervical ribs are more prevalent in women than men.

Only 5–10 per cent are symptomatic[9]. Symptoms, if present, are either neurological, due to displacement and stretching of the lower roots of the brachial plexus, or vascular resulting from kinking of the subclavian artery as it is forced to pass over the anterior end of the rib. We noted, as has been reported elsewhere, that the vascular complications are almost always confined to complete ribs[10,11].

Neurological symptoms are most common, and pain is the commonest. It may be felt distally in the distribution of the ulnar or, rarely, median nerve, or be confined to the neck and supraclavicular area. It tends to be exacerbated by movement, for example carrying objects and repetitive manual skills. Paraesthesia and sensory changes are common complaints, and tend to occur in the fourth and fifth fingers, i.e. the C_8 distribution. Muscle weakness is less frequent but, when it occurs affects the small muscles of the hand—the T_1 root[12].

Pallor, coldness and upper limb claudication are early symptoms of vascular complications of a cervical rib These are due to narrowing of the subclavian artery. If complete occlusion occurs, crippling ischaemia may be followed by gangrene of the digits. Unilateral Raynaud's phenomenon is a well-known presentation. This is now regarded as being a manifestation of thrombo-embolic disease rather than a vasomotor disorder, and is the result of emboli which form on damaged intima at the site of compression[13].

Neurological signs are only present in advanced cases. Wasting is described in the small muscles of the hand and is usually irreversible.

The diagnosis of thoracic outlet compression is often difficult. Emphasis has been placed in the past on certain diagnostic manoeuvres of the upper limb which obliterate the radial pulse[14–16]. The value of these has been questioned, therefore they were not employed in the routine examination of our patients[17]. We did, however, find a good correlation between vascular involvement and reduced pressure or absent pulses in the affected limb when assessed in the neutral position.

Plain X-rays of the chest, thoracic outlet and cervical spine will confirm the diagnosis of a supernumerary rib. As only 5–10 per cent cause symptoms, investigations should be carried out to eliminate other causes of similar symptoms. Degenerative conditions of the cervical spine, lesions of the shoulder girdle and rheumatic disorders, such as neuritis, myositis, arthritis or tendinitis, should be considered. Angina may mimic the pain in the arm and a Pancoast lung tumour may present in this way.

Patients in our series with predominantly neurological symptoms fared better than those with vascular symptoms. In the former, 60 per cent claimed a complete recovery, and the remainder improvement (with the exception of one, who had already developed irreversible nerve damage and muscle wasting). Among the patients with vascular symptoms, even though most experienced improvement, only one was 'cured' completely. Clearly our sample is small, but the question is raised whether cervical rib excision alone is sufficient in these patients.

Accurate assessment of arterial damage in patients with vascular symptoms is essential. One difficulty is that after resection of the rib, the artery may, on inspection, appear normal but have suffered internal damage. Even if arteriograms are performed, they often underestimate the degree of intimal involvement. We failed to cure completely most of our patients with vascular involvement. Some surgeons advocate careful operative inspection of the artery to stage the disease adequately, claiming that arteriograms are of no use in demonstrating intimal damage[18]. In 1934, Lewis and Pickering proposed a series of stages in the progression of the vascular damage Compression may lead first to stenosis, then post-stenotic dilatation (stage I); aneurysm formation, intimal damage and mural thombosis (stage II); and at any stage, the picture may be complicated by embolization and thrombosis (stage III)[19]. Scher *et al.* divided this progression into the stages shown and suggested the following guidelines for treatment: stage I, rib resection only; stage II, arterial resection or repair as well as rib resection; stage III, embolectomy, thrombectomy and arterial reconstruction and rib resection[20]. A similar policy of treatment was adopted in this series. Although small in numbers, our results would seem to indicate that a more aggressive approach towards identifying stage II disease should be made.

Acknowledgements

Figure 3 was prepared in the Department of Medical Illustration, University of Manchester, UK

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Inflow site: its effect on femoropopliteal and distal graft patency

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In a series of 245 vein grafts, results of 163 from the common femoral artery were compared with 82 from the proximal superficial femoral artery. Groups were comparable for risk factors, except that significantly more of the superficial femoral artery group were anastomosed to a single calf vessel ($P<0{\cdot}02$)*. Early technical failure was similar in both groups (14 per cent common femoral artery, 12 per cent superficial femoral artery,* P = *n.s.). Cumulative life table patency rates at 1 and 3 years were 77 per cent and 72 per cent in common femoral artery grafts, and 80 per cent and 70 per cent in superficial femoral artery grafts* (P = *n.s.). Analysis of 92 veins* in situ *(65 common femoral artery and 27 superficial femoral artery) showed 1-year patency rates of 75 per cent in common femoral artery grafts and 79 per cent in superficial femoral artery grafts* (P = *n.s.). These results suggest that the proximal superficial femoral artery is a safe inflow site for distal bypasses.*

Keywords: Distal bypass, inflow site, *in situ* bypass

The success of reversed and *in situ* methods of autogenous vein bypass grafting in lower limb occlusive disease is established. In a previous report[1], as with other authors[2,3], our results of both techniques have been similar. Traditionally, the common femoral artery (CFA) has served as the inflow site[4,5]. However, due to a short vein[3,6] or previous operative scarring, direct anastomosis to the CFA may not be possible. An extension or a more distally sited proximal anastomosis is therefore required.

We have used the proximal superficial femoral artery (SFA) with or without endarterectomy as the take-off site for distal grafts, when CFA could not easily be reached. This paper outlines the effect of this policy.

Methods

Between 1979 and 1984, 351 femoropopliteal and femorodistal grafts were performed Of these, 28 were lost to follow-up, 10 were for aneurysm, 7 originated from a synthetic graft and 61 were to an above-knee popliteal artery The remaining 245 grafts (229 patients) to the below-knee popliteal or crural vessels form the basis of this study Standard operative procedures were used, and the *in situ* technique used was similar to that described by Galland[7]. The CFA was used as take off site whenever possible (group I) and the remainder had their inflow from the proximal SFA (group II). Graft patency was determined by regular clinical examinations and ultrasound scanning (and an arteriogram if doubtful). Patency rates were determined using life table analysis (log rank test). The difference between groups was calculated using χ^2 with Yates' correction

Results

There were 163 grafts in group I (CFA) and 82 in group II (SFA). *Table 1* summarizes the demographic data. Thirty-one per cent (50) in the CFA group and thirty-two per cent (26) in the SFA group required endarterectomy at the proximal anastomosis. Distal anastomosis was to the below-knee popliteal artery in 93 per cent (151) of the CFA group and 82 per cent (67) of the SFA group. The remaining 7 per cent (12) of CFA and 18 per cent (15) of SFA grafts were to a single calf vessel ($\chi^2=5{\cdot}57$, $P<0\ 02$).

Immediate failure rates were 14 per cent (23) for the CFA group and 12 per cent (10) for the SFA group (P=n.s.). One- and three-year cumulative patency rates (*Figure 1*) were 77 per cent and 72 per cent in the CFA group and 80 per cent and 70 per cent in the SFA group, respectively (P=n.s.). Overall, 38 limbs in the CFA group and 8 in the SFA group came to major amputation.

Table 1 *Patient demographic data*

	Total (n=245)	Common femoral artery (n=163)	Superficial femoral artery (n=82)
Mean age (range) in years	67 (37–90)	66	69
Sex (male/female)	181/64	117/46	64/18
Diabetes	42 (17)	27 (17)	15 (18)
Indication for surgery			
Rest pain	151 (62)	99 (61)	52 (63)
Claudication	94 (38)	64 (39)	30 (37)
Arteriographic run-off			
(0–1) Vessel	49 (20)	29 (18)	20 (24)
(2–3) Vessels	196 (80)	134 (82)	62 (76)
Type of graft			
In situ vein	92 (38)	65 (40)	27 (33)
Reversed vein	153 (62)	98 (60)	55 (67)

P values were not significant in all cases Values in parentheses are percentages except in the patient age category

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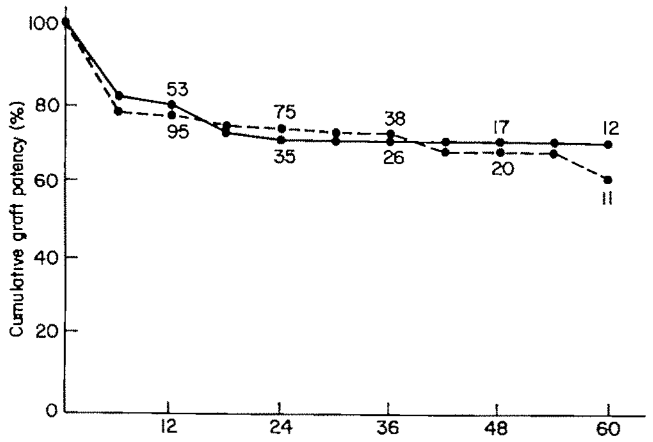

Figure 1 *Cumulative patency for all grafts (figures indicate number of grafts at risk). ---, Common femoral artery group; ——, superficial femoral artery group;* P>0·9

Table 2 *Patient distribution in the* in situ *group*

	Common femoral artery ($n=65$)	Superficial femoral artery ($n=27$)
Mean age in years	70	70
Sex (male/female)	44/21	20/7
Diabetes	12 (18)	2 (7)
Indication for surgery		
Rest pain	40 (62)	19 (70)
Claudication	25 (38)	8 (30)
Arteriographic run-off*		
(0–1) Vessel	11 (17)	11 (41)
(2–3) Vessels	54 (83)	16 (59)
Endarterectomy at proximal anastomosis	17 (26)	9 (33)
Distal anastomosis		
Popliteal artery (below-knee)	57 (88)	20 (74)
Crural artery	8 (12)	7 (26)

Values in parentheses are percentages * $P<0.03$ for arteriographic run-off, otherwise no significant differences between the common femoral artery group and the superficial femoral artery group

The *in situ* vein grafts, the particulars of which are summarized in *Table 2* (92 grafts: 65 CFA and 27 SFA), showed identical immediate failure rates of 11 per cent in both groups. Twelve-month patency (*Figure 2*) was 75 per cent in the CFA group and 79 per cent in the SFA group ($P=$n.s.). Fourteen limbs in the CFA group and two in the SFA group came to amputation.

Discussion

Traditionally, during distal bypass grafting, the CFA has been regarded as the optimal proximal anastomosis site. This is primarily based on the concern that more distal arteries are often affected or have a propensity to become involved by atherosclerosis[5,8,9]. Therefore, anastomosis distal to the CFA has been thought to compromise graft patency[5,9,10]. However, sporadic reports have challenged this view in selected cases by showing equally good results from both SFA and CFA[11]. In this series, whether diseased (endarterectomized) or not and despite a higher proportion of risk factors, inflow from the SFA has resulted in patency similar to that for the CFA.

More than 25 per cent of the long saphenous veins are too short for CFA anastomosis in vein grafting *in situ* without significant tension[3,6]. Although mobilizing the proximal vein may add some length, most surgeons advocate harvesting with a cuff or a tongue of the common femoral vein[4,10,12]. The former disrupts the vasa vasorum, which may negate one of the theoretical advantages of *in situ* methods[10], and the latter may increase morbidity[12,13]. The alternative is anastomosis to the proximal SFA.

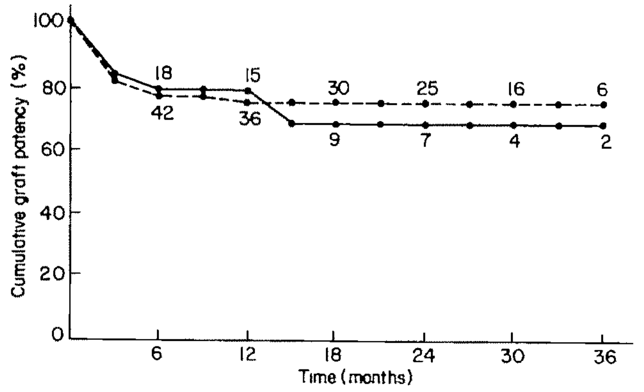

Figure 2 *Cumulative patency for* in situ *grafts (figures indicate number of grafts at risk) ---, Common femoral artery group, ——, superficial femoral artery group,* P>0·8

Although the retrospective nature of this study prevents conclusive statements, our data clearly suggest that using the proximal SFA as an inflow does not jeopardize the patency of the graft.

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Calf pump function in patients with healed venous ulcers is not improved by surgery to the communicating veins or by elastic stockings

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Calf muscle pump function was assessed in 41 limbs after venous ulcers had healed. Treatment was then randomized either to ligation of incompetent lower leg communicating veins and ablation of incompetent superficial veins combined with permanent graduated compression elastic stockings, or to graduated compression elastic stockings only. Half volume refilling time ($TV_{1/2}$) *and relative expelled volume* (EV_{rel}) *measured on foot volume plethysmography were used to assess calf muscle pump function. This was repeated after 12 months. The initial* $TV_{1/2}$ *and* EV_{rel} *were significantly lower than for normal limbs. There was no significant improvement in* $TV_{1/2}$ *in either treatment group (Student's* t *test,* $P=0{\cdot}78$, $P=0{\cdot}19$). EV_{rel} *did not improve significantly in limbs treated with elastic stockings alone* ($P=0{\cdot}94$)*, but there was a slight but significant improvement in* EV_{rel} *in limbs treated with surgery and elastic stockings* ($P=0{\cdot}048$)*; however, this was still significantly below the normal range* ($P<0{\cdot}001$)*. In limbs without phlebographic evidence of post-thrombotic changes, treated with the combination of surgery and elastic stockings, there was a significant improvement in* EV_{rel} ($P=0{\cdot}035$)*, but no improvement was found in limbs with post-thrombotic changes. This small but significant improvement in* EV_{rel} *in limbs without post-thrombotic changes treated by surgery and elastic stockings may explain the reduced incidence of reulceration that has been found following surgical eradication of the superficial and communicating veins.*

Keywords: Venous ulcer, communicating veins, calf pump

An inefficient calf muscle pump is thought to be the major underlying abnormality in limbs with venous ulceration[1] This may result from incompetence of the valves in the deep veins of the leg, in the lower leg communicating veins or in the saphenous veins and their tributaries. Consequently, treatments designed to reduce the incidence of recurrent venous ulceration aim to improve the efficiency of the calf muscle pump.

The two main methods of treatment currently employed are graduated compression elastic stockings[2], and ligation of incompetent lower leg communicating veins combined with eradication of incompetent saphenous veins and their tributaries[3]. Surgery is thought to improve the efficiency of the calf muscle pump by preventing venous reflux from the deep to the superficial veins through incompetent communicating veins[4] Graduated compression elastic stockings are thought to improve the calf muscle pump by increasing the interstitial pressure in the superficial tissues, thereby reducing the transmural pressure in the vessels within the superficial tissues[5].

A number of early studies reported good results in preventing recurrent venous ulceration following surgery to the communicating veins[6–9]; however, subsequent studies have reported disappointingly high rates of recurrent ulceration[10,11]. Assessments of calf muscle pump function after surgery, using foot vein pressure measurements on exercise, failed to show a significant improvement in limbs with post-thrombotic changes or incompetent lower leg communicating veins[12].

The ability of graduated compression elastic stockings to reduce the incidence of reulceration has not been tested in a controlled trial. However, wearing graduated compression elastic stockings for 3 months has been reported to improve the foot vein pressure fall on exercise[13]. This improvement was demonstrated when the tests were performed with the patient wearing the stockings, and also when the stockings were removed. This sustained improvement in calf muscle pump function after removing the elastic stockings implies that the stockings reverse valvular incompetence.

The aim of this study was to determine whether ligation of incompetent communicating veins and ablation of saphenous veins and their tributaries combined with wearing graduated compression elastic stockings, or wearing graduated compression elastic stockings alone, improved the efficiency of the calf muscle pump. The results were assessed 1 year after the start of treatment.

Patients and methods

Patients were studied after their ulcers had healed Only patients with definite venous ulcers were included A detailed history was taken and the legs were carefully examined. The following investigations were made to exclude other causes of ulceration: haemoglobin, the erythrocyte sedimentation rate, urea and electrolytes, liver function tests, blood glucose, Rose–Waaler titre, rheumatoid factor latex fixation test, antinuclear antibody titre and arterial Doppler ankle/brachial pressure index. All limbs were examined by ascending phlebography using the technique described by Lea Thomas[14], and popliteal vein reflux was assessed using a directional Doppler probe

Calf muscle pump function was assessed by foot volume

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plethysmography using a modification of the method described by Norgren[15] The equipment consists of a Perspex box filled to a predetermined level with water at 30°C. Alterations in water level in the box were detected by the difference in resistance between two electrodes. This was amplified and passed to a paper recorder To perform the test, patients removed their elastic stockings and placed their foot in the water bath. The volume of the foot was calculated. A baseline tracing was made and calibration was performed using a 10 ml syringe. The patient performed 20 knee bends and then stood still while a tracing of the change in the volume of the foot was made.

From this tracing (*Figure 1*), the expelled volume (EV) and the half volume refilling time ($TV_{1/2}$) were calculated. The expelled volume gives an assessment of the pumping function of the calf muscle, and the half volume refilling time gives an assessment of venous reflux. In order to allow for the differences in foot volume, the expelled volume is divided by the foot volume to obtain the relative expelled volume ($EV_{\rm rel}$).

The test was repeated with a pneumatic tourniquet at 100 mmHg, applied below the knee and then above the knee. The initial abnormalities remain after the application of tourniquets in patients with incompetence of the deep veins or the lower leg communicating veins. However, with long saphenous incompetence alone there is a return to normal with the application of a tourniquet above the knee, and with short saphenous incompetence a below-knee tourniquet has a similar effect. Normal ranges for $EV_{\rm rel}$ ($1\cdot5 \pm 0\cdot5$ ml/100 ml) and $TV_{1/2}$ (25 ± 10 s) have already been established in our department[16].

Foot volumetry has previously been shown to correlate well with the venous pressure fall on exercise[15,17], and has the advantage that it is non-invasive and patients are willing to return for repeat measurements.

Patients were randomized into two treatment groups after the initial investigations were performed. One group was treated by ligation of incompetent communicating veins—including lower leg communicating veins and incompetent long or short saphenous veins with an attempted eradication of all surface tributaries. These patients were all prescribed permanent below-knee graduated compression elastic support stockings (Sigvaris). The other group was treated with below-knee graduated compression elastic stockings alone Two new pairs of elastic stockings were supplied every 6 months.

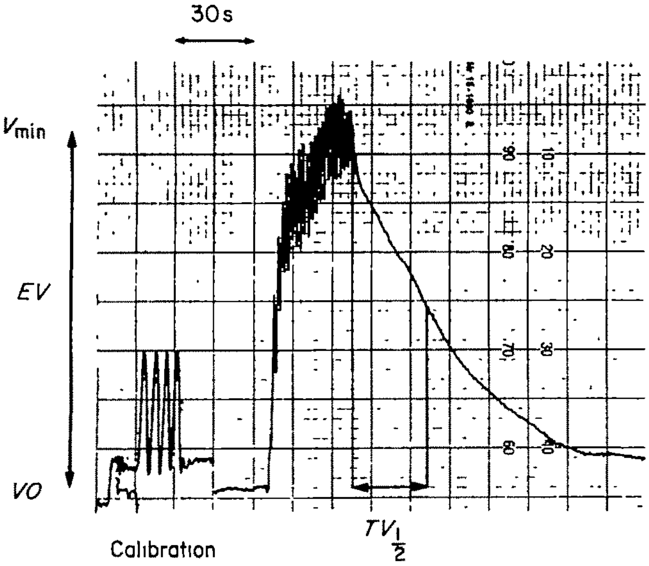

Figure 1 *Tracing of foot volume plethysmography performed on a normal limb, demonstrating the calculations made to obtain the expelled volume* (EV), *and the half volume refilling time* ($TV_{1/2}$)

Twelve months after entry into the study, the foot volumetry was repeated in those limbs remaining healed Six patients who developed recurrent ulceration within 12 months were treated with out-patient dressings and stopped wearing their elastic stockings: these patients were therefore withdrawn from this study. One of these patients was in the surgery and elastic stocking treatment group and five were in the elastic stocking only group.

Results

Of the 30 patients in whom a total of 41 limbs were assessed, 17 were men and 13 were women; their ages ranged from 38 to 80 years, with a median age of 61 years. Twenty limbs were treated by elastic stockings and surgery, and twenty-one limbs were treated by elastic stockings alone.

There was no significant difference in the ages of either group (medians 60 and 59 years). The incidence of post-thrombotic changes on ascending phlebography was similar in both treatment groups (*Table 1*), as was the incidence of popliteal vein reflux on Doppler assessment (*Table 1*)

All limbs had an abnormal half volume refilling time on the initial examination. The mean $TV_{1/2}$ and $EV_{\rm rel}$ were similar for both treatment groups and were significantly lower than for normal limbs (Student's *t* test, $P<0\cdot01$, $P<0\cdot01$, *Figure 2*).

The repeat $TV_{1/2}$ did not improve significantly for either treatment group (surgery and stockings, $P=0\cdot78$; stockings only, $P=0\cdot19$; paired Student's *t* tests, *Figure 3*), nor was there any significant improvement in the $EV_{\rm rel}$ for limbs treated by stockings alone ($P=0\cdot94$, *Figure 4*).

There was a small but significant improvement in the $EV_{\rm rel}$ in limbs treated by surgery and elastic stockings ($P=0\cdot048$, *Figure 4*). The repeat $EV_{\rm rel}$ for these limbs was still significantly lower than for normal limbs ($P<0\cdot001$, *Figure 4*).

Limbs with phlebographic evidence of post-thrombotic changes were considered separately from those with normal deep veins. For the limbs treated with surgery and elastic stockings, there was a significant improvement in the $EV_{\rm rel}$ in limbs with normal deep veins ($P=0\cdot035$), but no significant improvement in limbs with post-thrombotic changes ($P=0\cdot66$, *Figure 5*). $TV_{1/2}$ did not improve significantly in limbs with or without post-thrombotic changes ($P=0\cdot44$, $P=0\cdot92$, respectively). In limbs treated with elastic stockings only, there was no significant improvement in $TV_{1/2}$ with or without post-thrombotic changes ($P=0\cdot41$, $P=0\cdot53$, respectively), or in $EV_{\rm rel}$ for limbs with or without post-thrombotic changes ($P=0\cdot30$, $P=0\cdot46$, respectively).

Limbs with popliteal vein reflux on Doppler assessment were considered separately from limbs without popliteal vein reflux. In limbs treated with surgery and elastic stockings, there was no significant improvement in either $TV_{1/2}$ with ($P=0\cdot42$) or without popliteal vein reflux ($P=0\cdot97$), or $EV_{\rm rel}$ with ($P=0\cdot27$) or without popliteal vein reflux ($P=0\cdot13$). In those limbs treated with elastic stockings alone, similarly there was no improvement in either $TV_{1/2}$ with ($P=0\cdot54$) or without popliteal vein reflux ($P=0\cdot39$), or in $EV_{\rm rel}$ with ($P=0\cdot21$) or without popliteal vein reflux ($P=0\cdot33$).

Table 1 *Changes on ascending phlebography, and assessment of popliteal vein reflux on directional Doppler testing*

Treatment	Post-thrombotic changes	Incompetent communicating veins only	No abnormal veins
Surgery and stockings	8	7	5
Popliteal vein reflux	2	3	4
No popliteal reflux	6	4	1
Stockings only	10	4	7
Popliteal vein reflux	6	2	5
No popliteal reflux	4	2	2

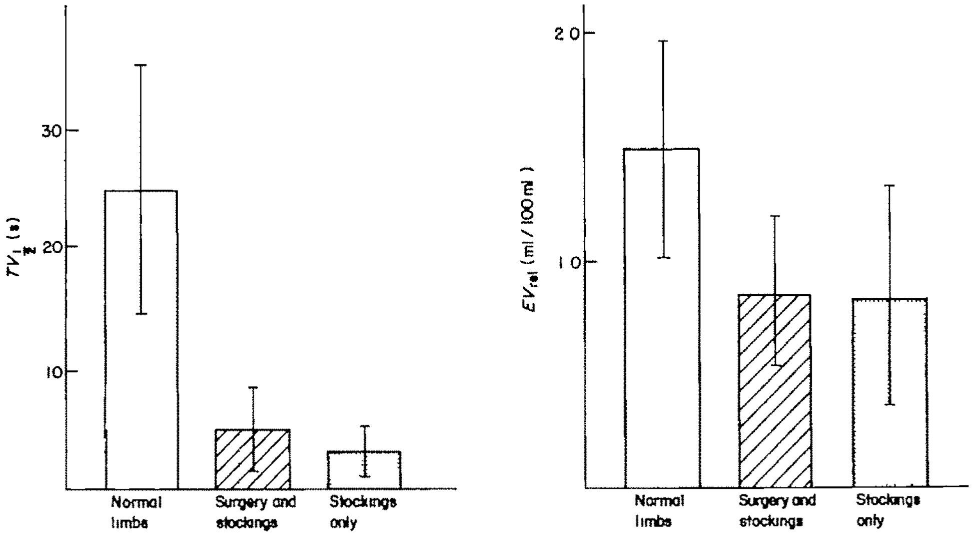

Figure 2 *Initial* $TV_{1/2}$ *and* EV_{rel} *for the two treatment groups. The initial levels were significantly lower than those for normal limbs (Student's* t *test,* $P<0{\cdot}01$ *for each group)*

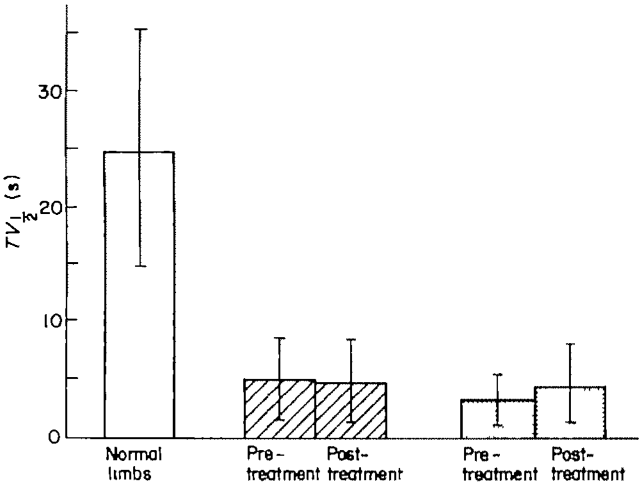

Figure 3 *Repeat* $TV_{1/2}$ *for each treatment group. There was no significant improvement in either treatment group:* $P=0{\cdot}78$, $P=0{\cdot}19$ *respectively (paired Student's* t *test).* ■, *surgery and stockings,* ☐, *stockings only*

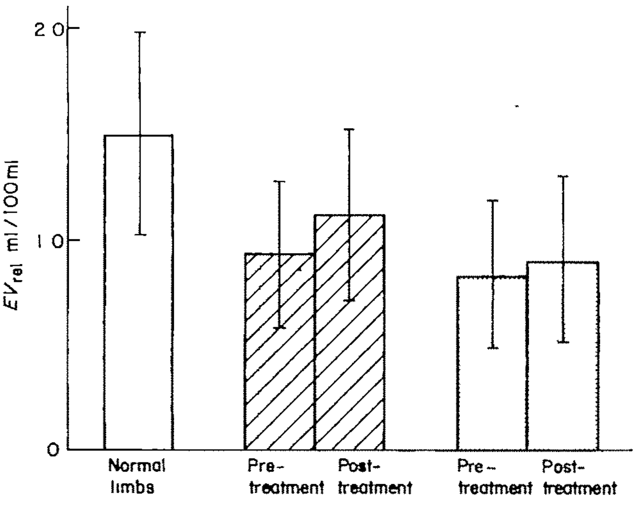

Figure 4 *Repeat* EV_{rel} *for each treatment group. There was a significant improvement in the surgery and stockings* (■) *group* ($P=0{\cdot}048$)*, but not in the stockings only* (☐) *group* ($P=0{\cdot}94$)

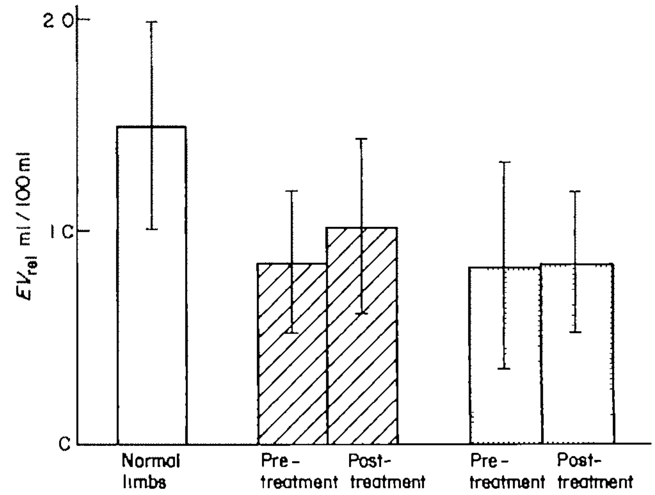

Figure 5 *Repeat* EV_{rel} *in the surgery and stockings group, separated into limbs with* (■) *and limbs without* (☐) *post-thrombotic changes on ascending phlebography. There was a significant improvement in those limbs with normal deep veins* ($P=0{\cdot}035$)*, but not in those with post-thrombotic changes* ($P=0{\cdot}66$)

Discussion

The demonstration of abnormal venous reflux (as measured by $TV_{1/2}$) and an abnormal pumping function of the calf muscle (as measured by EV_{rel}) in patients with healed venous ulcers, confirms the findings of previous studies[15,17].

A distinction between post-thrombotic changes in the deep veins and incompetent lower leg communicating veins cannot be made using foot volume plethysmography. All patients in this study had abnormal findings on foot volume plethysmography, indicating either post-thrombotic changes in the deep veins or incompetent lower leg communicating veins; however, ascending phlebography failed to demonstrate either abnormality in 12 of the 41 limbs. This highlights the difficulty sometimes found in deciding what constitutes post-thrombotic changes on ascending phlebography, and the need for further assessment using varicograms to establish the presence of incompetent lower leg communicating veins.

We were unable to demonstrate any improvement in either venous reflux ($TV_{1/2}$) or the pumping function of the calf muscle (EV_{rel}) after patients had worn graduated compression elastic stockings for 12 months. Sommerville *et al.*[13] found an improvement in foot vein pressure fall on exercise after elastic stockings had been worn for 3 months. This improvement was found when pressures were measured with the patients wearing the stockings, and when the test was repeated after the stockings had been removed. This implied that the elastic stockings improved the valvular competence of the leg veins. Our results cast doubt on their observations.

We were able to demonstrate a small but significant improvement in the EV_{rel} in limbs treated by surgical eradication of surface varicosities and ligation of incompetent communicating veins combined with elastic stockings. This did not return to the normal range and there was no equivalent improvement in the $TV_{1/2}$ in these limbs. These findings suggest that treatment with surgery and elastic stockings improves the pumping function of the calf muscle but venous reflux is not altered.

The improvement in EV_{rel}, after treatment with surgery and elastic stockings, was found only in limbs with normal deep veins on ascending phlebography. This may in part explain why surgical ligation of incompetent communicating veins may be effective in preventing reulceration in limbs without evidence of post-thrombotic changes on phlebography[3,11].

The failure to demonstrate any improvement in either EV_{rel} or $TV_{1/2}$ in limbs with popliteal vein reflux, or limbs without popliteal vein reflux, in both treatment groups, suggests that the presence or absence of popliteal vein reflux is not a good predictor of which limbs will subsequently reulcerate.

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Incidence of deep vein thrombosis after major abdominal surgery in Brisbane

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There is some evidence that postoperative deep vein thrombosis (DVT) may be commoner in cool than in warm climates. To determine whether this complication is less common in the subtropical climate of Brisbane than in more temperate locations, the incidence of DVT after major abdominal surgery was assessed by ^{125}I fibrinogen scanning. In order to avoid overestimating the incidence of DVT, abnormal scans were accepted as diagnostic only if the DVT was confirmed by venography or if the abnormality on the scan fulfilled more stringent criteria than have previously been applied. Thirty-six of 152 patients (24 per cent) developed a DVT; this incidence was significantly lower than in one previous study from Melbourne and higher than that found in South-East Asia and East Africa, but was not significantly different from that reported from Sydney, Japan and several centres in North America and Britain. There was no apparent seasonal variation in the incidence of the complication. The geographical variation in incidence of postoperative DVT may have been overestimated in previous reports and may be at least partly due to variations in screening technique.

Keywords: Postoperative complications, thrombo-embolism, thrombophlebitis, diagnosis, fibrinogen, radiology

There may be a geographical variation in the incidence of deep vein thrombosis (DVT) after general surgical operations. Several studies have demonstrated a high incidence of postoperative DVT diagnosed by ^{125}I fibrinogen scanning in the UK[1-3], while similar studies from Japan[4], Malaysia[5], Hong Kong[6] and Africa[7] have suggested a much lower incidence of this complication in these areas. In Australia there is evidence that postoperative DVT is less common in Queensland than in the cooler Southern States[8,9]. The complication may also be commoner in winter than in summer[10], suggesting a possible climatic basis for these geographical variations. However, the climatic hypothesis is not substantiated and the evidence for a true geographical variation is weakened by reports that postoperative DVT in some parts of the UK was substantially lower than that in London[11], and that DVT could be demonstrated by a venographic screening in 53 per cent of patients after hip surgery in Hong Kong[12]—an incidence similar to that in the UK and North America. It is not clear whether the reported differences reflect true geographical and chronological variations or are due to methodological inconsistencies.

The present study was undertaken to determine as accurately as possible the incidence of postoperative deep vein thrombosis in Brisbane in a high-risk group of patients similar to those studied in Britain[13]. The aims were to provide objective evidence to assist in resolving the controversial issue of whether prophylaxis against DVT should be used in this community, and to accumulate a data base for use in possible future controlled studies of prophylactic techniques.

Patients and methods

All patients over the age of 40 years having a laparotomy or more major abdominal surgery at the Princess Alexandra Hospital were eligible for admission to the trial. Patients with a previous history of thrombo-embolic disease were excluded, as were those having anticoagulants intra-operatively. No patient entered into the study was to have DVT prophylaxis in the form of heparin, other anticoagulants or support stockings. The trial was approved by the Hospital Ethical Committee; it was considered reasonable to withhold DVT prophylaxis from these patients as such prophylaxis is not customary at this hospital at the present time. All patients studied gave informed consent.

Patients were screened for DVT by ^{125}I fibrinogen scanning. The thyroid gland was blocked pre-operatively by potassium iodide (160 mg) given orally and continued on a daily basis for one month. One hundred microcuries of ^{125}I-labelled human fibrinogen (Amersham) was given intravenously 4 h after the first dose of potassium iodide. A pre-operative scan was carried out at least 1 h later and subsequently scans were carried out on the first, third, fifth and seventh postoperative days. Radioactive counts were recorded at 2-inch (≈51 mm) intervals along the thigh and calf of each leg as described by Flanc *et al.*[1], using a Pitman model 235 isotope localization monitor as described by Kakkar *et al.*[2,14]. Scans were carried out with the legs elevated to reduce venous pooling and to give access to the calf for scanning. Radioactive counts at each point in the leg were expressed as a percentage of counts obtained over the heart when the scintillation counter was placed over the precordium[14]; a scan was considered abnormal if the counts at any point on the leg were increased by 20 percentage points or more over those recorded at the same point on the previous scan, and if the elevation of 20 points over the index scan was sustained in the subsequent scan[15]. Counts measured at the uppermost site on each leg were disregarded because the proximity of this site to the femoral artery makes counting unreliable in detecting venous disease here. All patients were reviewed on a daily basis postoperatively to detect symptoms and signs of thrombo-embolic disease (calf tenderness or swelling, pleuritic chest pain, haemoptysis or dyspnoea).

Patients with abnormal fibrinogen scans underwent ascending venography on the side of the abnormal scan whenever possible. All venograms were carried out by a consultant radiologist (J.H.) with a special interest in the study with a particular view to demonstrating the deep veins of the calf. Many additional film exposures were often necessary to ensure that all axial deep veins in the calf were filled with contrast. All venograms were considered technically adequate. All normal venograms were reviewed by the radiologist and checked by a second consultant radiologist. As a result one venogram initially thought to show no thrombus was reclassified as demonstrating a small thrombus. Bilateral ascending venography was not used routinely. An abnormal fibrinogen scan with venous thrombus visualized on subsequent venography was considered definitive evidence of DVT. When venography either was not done or was normal, an abnormal scan was considered to prove a DVT only when stringent criteria were met: the patient must not have any condition capable of producing a

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false positive scan (superficial thrombophlebitis, local haematoma, a local incision, ulceration, cellulitis, arthritis, gross oedema[16] or varicose veins[17]), and the scan must be unequivocally abnormal. In this context an unequivocally abnormal scan was defined as one in which a 20-point increase in counts occurred at two adjacent positions on the leg, with counts continuing to increase at both positions on at least the next scan, or one in which counts increased by 20 percentage points at one position and subsequently continued to increase at that position on all further scans. These unusually stringent criteria were adopted to ensure that the incidence of DVT was not overestimated.

Results

Two hundred and six patients were entered into the study. Thirty-nine were subsequently excluded from further consideration: one patient had an epigastric hernia repair and did not meet the entry criteria for the study; in two other patients counts in the leg postoperatively were too low for accurate evaluation because of operative blood loss and thirty-six were discharged from hospital before completing the fibrinogen scanning protocol. All 36 patients in this group had fewer than three postoperative scans. Of the remaining 167 patients, 15 received low-dose subcutaneous sodium or calcium heparin perioperatively despite having been entered into the trial. These patients were therefore also excluded from further consideration although in four of them (27 per cent) postoperative venous thrombosis was detected by fibrinogen scanning and confirmed by venography.

One hundred and fifty-two patients who had completed the protocol without violation were available for study. There were 89 men and 63 women with a mean age of 62·5 years (range 40–89). The operations performed are shown in *Table 1*. Fifty-eight patients (38 per cent) developed abnormal fibrinogen scans postoperatively (*Figure 1*). Twenty-seven of these had DVT confirmed by venography. Twelve had no venogram: five refused; four were too ill; one was allergic to iodinated contrast media; one had a pulmonary embolus diagnosed and was anticoagulated before venography could be carried out; and one had an abnormal scan which was not recognized until after he left hospital. Two more patients had venograms performed inadvertently only on the contralateral side to the abnormal scan. Of these 14 patients, six (including the patient with the pulmonary embolus) had scans sufficiently abnormal to be considered diagnostic of DVT by the stringent criteria previously described (*Figure 1*). Seventeen patients with abnormal scans had no DVT dectectable by venography: six of these had varicose veins; two had leg ulcers; two had severe bilateral oedema (one due to congestive heart failure and one due to hypoalbuminaemia); and one had venous distortion (thought to be a result of an old and previously unsuspected DVT) at the site of the positive scan, but no new thrombus Of the remaining six patients only three had scans considered to meet the strict criteria for diagnosis of DVT (*Figure 1*). These three patients had all been in hospital for more than 5 days preoperatively, and two of them had malignant disease. It was assumed that the abnormal scans in these three patients reflected small amounts of thrombus in non-axial calf veins, which are difficult to detect by venography[14].

A final diagnosis of DVT was thus made in 36 patients (24 per cent of the study group). There were 20 men and 16 women with a mean age of 65·2 years (range 42–87) The operations they had are shown in *Table 1*. Physical signs of DVT were uncommon in this group. Calf tenderness was observed postoperatively in six, one had slight unilateral oedema, and another, already referred to, developed pleuritic chest pain and dyspnoea due to a pulmonary embolus. This was the only patient in the present series who would have been strongly

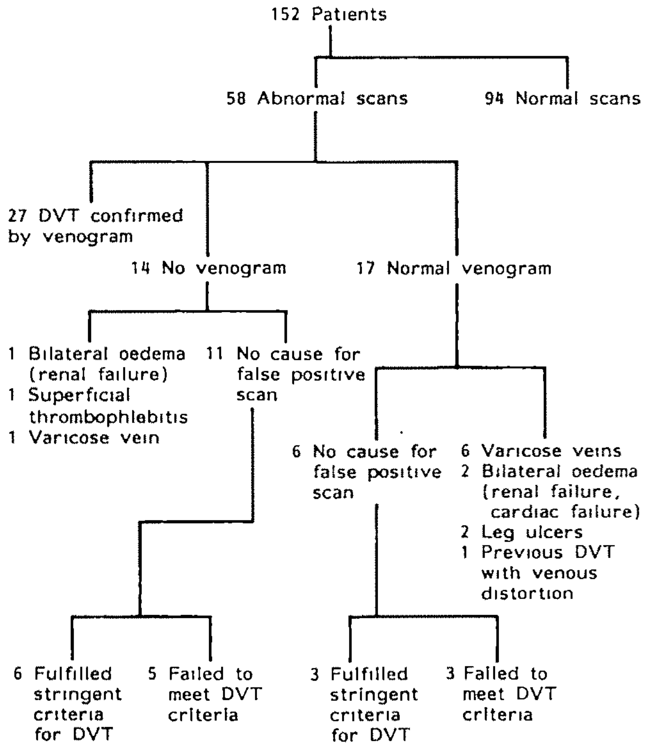
152 Patients
58 Abnormal scans
94 Normal scans
27 DVT confirmed by venogram
14 No venogram
17 Normal venogram
1 Bilateral oedema (renal failure)
1 Superficial thrombophlebitis
1 Varicose vein
11 No cause for false positive scan
6 No cause for false positive scan
6 Varicose veins
2 Bilateral oedema (renal failure, cardiac failure)
2 Leg ulcers
1 Previous DVT with venous distortion
6 Fulfilled stringent criteria for DVT
5 Failed to meet DVT criteria
3 Fulfilled stringent criteria for DVT
3 Failed to meet DVT criteria

Figure 1 *Outcome in the 152 patients available for analysis*

Table 1 *Operations performed and DVT according to procedure*

Procedure	Number performed in all patients entered into study	Number performed in patients who completed study protocol	Patients with DVT (percentage of evaluable patients)
Cholecystectomy	93	55	14 (25%)
Colorectal resection			
Colectomy	32	28	6 (21%)
Anterior resection	8	4	—
Abdominoperineal resection	3	2	—
Gastrectomy	12	12	5 (42%)
Vagotomy	5	5	2 (40%)
Fundoplication	4	4	—
Biliary bypass (malignant disease)	8	8	2 (25%)
Hepatectomy	6	5	2 (40%)
Pancreatectomy	2	2	—
Splenectomy	1	1	—
Oesophagectomy	1	1	—
Nephroureteric procedures	4	4	1 (25%)
Incisional hernia repair	5	4	—
Miscellaneous	22	17	4 (24%)

suspected of having thrombo-embolic disease on clinical grounds only. In comparison, two of the 116 patients finally diagnosed as having no DVT had calf tenderness, two others were thought to have some calf induration, three others complained of calf pain and three had bilateral ankle oedema.

Thirty-four of the thirty-six DVT occurred in the calves, but two patients appeared to have involvement of the thigh veins only (one delineated by scanning and the other visualized on venography). There were no evident seasonal variations in the frequency of DVT (*Figure 2*)

Discussion

The incidence of postoperative DVT observed in this study is significantly higher ($\chi^2 = 4{\cdot}31$; $P < 0{\cdot}05$) than that noted in a previous study of postoperative DVT in Brisbane (9 of 75 patients or 12 per cent) when ^{125}I fibrinogen scanning was also the major screening technique used to detect thromboses[8]. Apart from the interval of 14 years between the two studies, the most obvious way in which they differed was in the population of patients studied. The earlier investigation showing a lower incidence of DVT accrued patients undergoing all forms of general surgery, including operations of lesser magnitude like hernia repairs, whereas in the present report only patients who had more major surgery are considered. The finding of a higher incidence of DVT after more major abdominal surgery is consistent with the observations of others[14,15].

The incidence of abnormal fibrinogen scans in the present study is compared in *Table 2* with previous reports. Postoperative DVT diagnosed by this technique in our patients was significantly less common than in one study in Melbourne[8], and significantly commoner than in Malaysia[5], Hong Kong[6] and the Sudan[7]. The incidence of DVT we observed was not significantly different from that reported in previous studies in miscellaneous general surgical patients in London[1,2], other parts of the UK[11], and North America[15], and in patients having major abdominal surgery in Japan[4]. It was also strikingly similar to the frequencies of 27 per cent and 24·4 per cent recently reported after major surgery in the north of England[18] and North America[19] respectively.

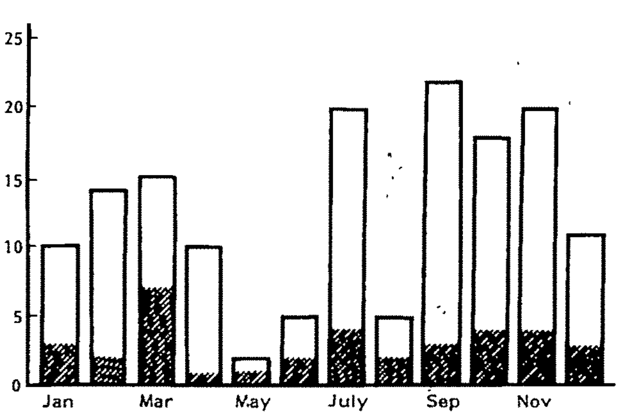

Figure 2 ▨ *Monthly incidence of DVT in relation to* ☐ *total numbers of patients studied*

The extremely high incidence of postoperative DVT reported from Melbourne[8] seems anomalous Unfortunately this report is difficult to evaluate critically because it took the form of a verbal presentation which was never subsequently published. As the incidence of postoperative DVT reported from Sydney in 1977[10] did not differ significantly from that reported here, and as we were unable to detect a seasonal variation in incidence of DVT in Brisbane, it seems unlikely that any difference in results between Brisbane and Melbourne could be attributed to the cooler climate in the more southerly city. Differences in technique or criteria for interpretation of scans appear more plausible. Some earlier investigators have accepted more liberal criteria for positive fibrinogen scans than are generally in use at present. Negus *et al.*[20] originally accepted a sustained rise in percentage counts of 15 or more (instead of 20) as indicative of DVT, and in at least one subsequent investigation a single elevation of 15 was accepted as diagnostic[3]. Application of these criteria in the present study would have resulted in a dramatic increase in the number of DVT diagnosed. Even by the standard of a rise in percentage counts of 20 sustained for at least two consecutive scans, 58 of 152 patients in the present study had abnormal scans, which would have indicated a DVT incidence of 38 per cent if confirmatory venograms or more rigorous criteria for diagnostic scans had not been used. Had fibrinogen scans been carried out daily instead of on alternate days in the postoperative period, an even higher incidence of abnormal scans might have been observed.

Since the original validation studies of Negus *et al.*[20] and Kakkar and his colleagues[21] nearly 20 years ago, few investigators have attempted to verify abnormal fibrinogen scans routinely by venography. Instead there has been universal acceptance of a high correlation between the results of the two investigations—a phenomenon not notable in the present study. In *Table 3* the incidence of abnormal venograms in our patients is compared with those reported from other studies where venography was used 'routinely' in patients with abnormal scans. Thrombosis detected by venography was commoner in our patients than in Hong Kong[6] and Oklahoma[15], but no more common than in Japan[4]. The discrepancy between our venographic results and those reported from Oklahoma may reflect the fact that fewer patients with abnormal scans were submitted to venography in the North American (56 per cent) than in the present study (79 per cent). The paucity of reports in

Table 2 *Incidence of DVT in present and previous studies*

Study	DVTs/total no of patients	DVTs (%)	P (χ^2) (compared with present study)
Present study	36/152	24	—
Brisbane 1973[8]	9/75	12	<0·05
UK (London) 1969[1]	23/65	35	n.s.
UK (London) 1970[2]	6/18	33	n.s.
UK (Essex) 1971[11]	17/100	17	n.s.
Melbourne 1972[8]	38/81	47	<0·001
USA (Oklahoma) 1973[15]	34/200	17	n.s.
Sudan 1973[7]	12/100	12	<0·05
Malaysia 1974[5]	8/68	12	<0·05
Sydney 1977[10]	20/120	17	n.s.
Hong Kong 1980[6]	4/150	2·6	<0·001
Japan 1983[4]	49/256	15	n.s.
USA (Multicentre) 1985[19]	22/90	24	n.s.
UK (Leeds and Newcastle) 1986[18]	23/85	27	n.s.

Table 3 *Incidence of DVT proved by venography in present and previous studies*

Study	DVTs/total no. of patients	DVTs (%)	P (χ^2) (compared with present study)
Present study	27/152	17·7	—
USA (Oklahoma) 1973[15]	19/200	9·5	<0·05
Hong Kong 1980[6]	4/150	2·6	<0·001
Japan 1983[4]	37/256	14·4	n.s

which venography has been used routinely to confirm the results of ^{125}I fibrinogen scanning undoubtedly reflects the ethical and practical difficulties involved in submitting asymptomatic patients to an invasive investigation which may itself cause deep vein thrombosis[22,23].

The results presented here certainly do not rule out the possibility of a real geographical variation in incidence of postoperative DVT, but they do suggest that such a variation is less dramatic than indicated in some previous reports. Apparently minor variations in the technique and interpretation of fibrinogen scanning certainly occur[24] and may result in greater variation between studies than has been widely appreciated. As it is almost impossible to do venograms to confirm abnormal scan results in all patients unless numbers are very small, close comparison of the results of different investigations thus becomes difficult unless other screening modalities, like impedance plethysmography[25–27] and real-time ultrasound[28] have been used alongside fibrinogen scanning. The use of multiple screening techniques will certainly be desirable in future studies. The present study has provided no evidence to support the contention that postoperative DVT is less common in the warm climate of Brisbane than in Western Europe or North America. Our results therefore suggest that such a contention should no longer be used to support a policy of omitting DVT prophylaxis in our area.

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Clinical application of the cholecystokinin provocation test

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This paper reviews the value of administration of cholecystokinin (CCK) in the assessment of patients thought to have acalculous biliary pain. The literature contains conflicting reports and there is no unequivocal evidence to support the use of CCK provocation tests as a basis for deciding the need for cholecystectomy.

Keywords: Cholecystokinin, provocation tests, acalculous biliary pain, cholecystectomy

Cholecystokinin and gallbladder motility

In a series of experiments including cross circulation studies in dogs, Ivy and Oldberg first discovered and isolated a substance which caused contraction of the gallbladder[1]. They termed this substance cholecystokinin (CCK) After initial purification they administered bolus doses to volunteers including themselves[2]. With X-ray fluoroscopy they observed wide differences in the effect of this hormone on human gallbladder emptying. They also noted that some individuals experienced pain described as typical of gallbladder colic. At this time the hormone was given as a bolus injection, usually in a dose of 1 Ivy dog unit (IDU) per kg, over a period ranging from 30 s to 3 min A dog unit is the quantity of dried material which will increase the intragallbladder pressure of a dog by 1 cmH_2O within 3 min when injected intravenously.

Ivy had previously noted in one animal experiment in which the cystic duct was obstructed that administration of CCK caused the dog to salivate and become distressed[1]. This he interpreted as the development of pain and nausea following CCK. Ivy's enthusiasm for the use of CCK in clinical practice received a boost when 17 years after experiencing discomfort on injection of CCK he underwent cholecystectomy for gallstones[3]. He took this to mean that the pain he experienced during CCK induced contraction of his gallbladder indicated an abnormality of motility which subsequently led to the development of gallstones. CCK did not become commercially available until the late 1950s when Jorpes and Mutt developed a method of purifying the extract[4] Torsoli and his colleagues evaluated the purified preparation and noted, as had Ivy, that some volunteers experienced pain, not unlike biliary colic, on injection of CCK[5]. They suggested that CCK would be clinically useful for induction of gallbladder contraction during fluoroscopy, and raised the possibility that it might prove useful in the evaluation of acalculous biliary disease or gallbladder dyskinesia.

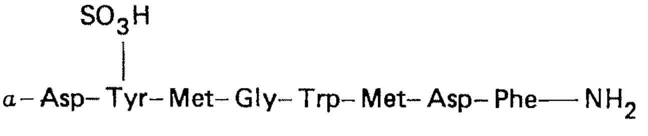
Biochemistry of cholecystokinin

Since the earliest studies it has been clear that the introduction of the products of digestion, particularly fat, into the duodenal lumen led to the release of CCK from the duodenal mucosa[1,6]. Plasma levels of CCK have been measured by radioimmunoassay and shown to rise after a meal[7,8]. The plasma changes noted are in phase with contraction of the gallbladder and relaxation of the sphincter of Oddi. Further, when physiological levels of CCK are achieved by low dose intravenous infusion active gallbladder contraction may be observed[9]. The half-life of CCK in the bloodstream is short at between 2·5 and 3·3 min[8,10] in common with most peptide hormones, and physiological levels can only be achieved by continuous infusions.

The active part of the CCK molecule is the C-terminal octapeptide chain and the biological activity of this segment depends upon the sulphate group attached to the tyrosine residue (*Figure 1*). *In vitro* animal studies have shown that loss of this sulphate group reduces the activity of CCK by about 150 times[6]. CCK is thought to act via specific cell membrane receptors and its effect on muscle is a direct one, independent of cholinergic or adrenergic mechanisms[11]. Further, Lennon and his colleagues[12] have shown *in vitro* that human gallbladders will respond to CCK in the presence of antihistamines. Amer and McKinney[13] have proposed that CCK stimulates phosphodiesterase activity. This leads to a decrease in the levels of intracellular cyclic AMP which is generally accepted to be the mediator controlling contraction in many forms of smooth muscle[14,15]. CCK is recognized to contract all gastrointestinal smooth muscle on direct exposure. This includes muscle from the sphincter of Oddi[16] and muscle from the lower oesophageal sphincter[17] in animals. In the intact animal both these structures relax when exposed to CCK in the bloodstream but after nerve conduction has been blocked by a neurotoxin such as tetrodotoxin, contraction is observed. This suggests a nervous control of these sphincters which can override the direct response to CCK in these sphincter zones

Effects of CCK administration on the biliary tract

It is clear that exogenous pharmacological doses of CCK can cause gallbladder contraction. It is also recognized that bolus administration of this hormone can cause pain and discomfort in normal individuals[18–22]. Contraction of the cystic duct and gallbladder neck region has been recognized radiologically[18,19] and *in vitro* studies of canine and human



$$\begin{array}{c}SO_3H\\ |\\ a-\mathrm{Asp}-\mathrm{Tyr}-\mathrm{Met}-\mathrm{Gly}-\mathrm{Trp}-\mathrm{Met}-\mathrm{Asp}-\mathrm{Phe}-NH_2\end{array}$$

Figure 1 *The amino acid residues found in the C-terminal octapeptide of cholecystokinin (CCK). The sulphate group is normally found on the tyrosine residue and in this position confers maximum activity to both the isolated octapeptide and the full CCK-33 molecule*

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gallbladders have shown that high doses of CCK cause contraction of cystic duct muscle[23,24]. The effect of CCK on the common bile duct is unknown although relaxation of the sphincter of Oddi is accepted as a normal response[25]. High doses of CCK cause 'paradoxical' contraction of the sphincter in animals[26] and similar responses have been demonstrated in patients[27,28]. Bolus administration leading to high peak serum levels may produce pharmacological rather than physiological responses within the normal biliary tract. Low dose infusions are thought by some to provide a stimulus more akin to the normal situation and Hopman and co-workers[22] showed that a given dose administered over 60 min, rather than 1 min, contracts the gallbladder more effectively. Other workers have demonstrated that intramuscular injections which provide a more sustained low serum level of CCK are more effective than intravenous bolus injections in causing gallbladder contraction[29,30].

Extra-biliary effects of CCK

The extrabiliary effects of CCK are many and varied. It is generally accepted that normally it increases pancreatic secretion of enzyme rich fluid[25]. In animal experiments it alters gastric acid secretion[31] and relaxes, via a neuronal mechanism, the lower oesophageal sphincter[17]. In animals and humans exogenous CCK causes a marked increase in the activity of both small[32] and large bowel[33]. As with other peptide hormones, receptors to CCK have been identified in the central nervous system[34]. Their precise function is not known but one acupuncture study suggests that they may have a role in pain perception[35].

CCK preparations

The different preparations of CCK available and used in practice have made comparison of work in this field difficult. CCK like most gastrointestinal hormones exists in a number of forms. A linear polypeptide of 33 amino acid residues (CCK-33) is considered to be the physiologically active hormone with a 39 residue polypeptide, possibly a prohormone (CCK-39), being less active. On a molar basis the C-terminal octapeptide (CCK-8) is 8–10 times more active *in vitro* than any of the larger molecules[6]. The extraction from porcine duodenum and separation method described by Jorpes and Mutt[4] yields a number of fractions with cholecystokinetic activity. One preparation based principally on the larger molecules CCK-33 and CCK-39 was marketed in this country by Kabi-Vitrum. This was relatively expensive (£15–20 per patient) and has recently been withdrawn possibly for commercial reasons. Another fraction is marketed as a British preparation called Pancreozymin (Boots, Nottingham, UK). This remains available (<£5 per patient) although it too is to be discontinued in the near future. Oliver and Harvey[36] have analysed both preparations and have shown that the biological activity of Pancreozymin relies largely on smaller peptide fragments and this preparation contains immunoreactive forms of CCK with little biological activity. This may be due to loss of the sulphate group in the active portion of the larger molecules as discussed above. In the same study they examined both the *in vivo* and *in vitro* behaviour of the Boots and the Kabi-Vitrum preparations, concluding that both were equally effective in causing contraction of the gallbladder. Some workers have used purified CCK-8 (Sincalide, Squibb) to induce gallbladder contraction[21,29,30,37]. At present CCK octapeptide is not available for clinical use in this country but with the withdrawal of the other preparations it may be the only alternative, albeit expensive (£85–100 per patient).

Caerulin is a decapeptide structurally similar to CCK-8 isolated from the skin of toads It is slightly less potent than CCK-8 but shares similar *in vivo* and *in vitro* characteristics[6,38]. Like CCK-8 it is not available for general clinical use in this country although there are reports of such use in Europe[39].

Acalculous biliary disease

It remains difficult to discriminate acalculous biliary disease from other conditions which may present with right hypochondrial pain[40–43], so much so that some surgeons will not entertain cholecystectomy without radiological or ultrasonic confirmation of biliary calculi Others are content to offer surgery on the basis of a 'good' history and an absence of alternative pathology. Historically the results of cholecystectomy in the absence of gallstones have been poor with up to 40 per cent of patients reporting no improvement after surgery[40,41,44]. In comparison it is accepted that 80–85 per cent of patients with appropriate symptoms and proven gallstones will be 'cured' by cholecystectomy[45]. Bodvall[46], however, reported painstaking follow-up of a large series from Sweden in 1964 and observed as little as 51 per cent symptomatic 'cure' in patients with cholelithiasis alone. If patients had experienced cholecystitis this figure rose to 70 per cent and if patients with postoperative dyspeptic symptoms and no pain were included there was an 80 per cent response to cholecystectomy

One explanation for the poor results in acalculous pain is that disease of the gallbladder is not causing the symptoms and therefore its removal is not the answer[47]. This may sometimes be the case but there appear to be patients who have gallbladder disease apparently unrelated to stones and who will benefit from cholecystectomy[40,43,48–51]. These patients may have calculi too small to be detected by conventional investigations or may be suffering from acalculous biliary disease. Faecal sieving which successfully detected missed stones in patients with pancreatitis[52] appears to have been neglected in patients with acalculous pain. The old diagnostic technique known as the Meltzer–Lyon test[53] which examined bile aspirated from the duodenum after induction of gallbladder contraction has been revived recently, although with conflicting results. Einarsson and colleagues[54] were unable to demonstrate any difference between bile samples from patients with acalculous pain and control subjects. Moskovitz's group[55], however, found both cholesterol and bilirubinate crystals in bile samples from patients with acalculous pain.

Confirmation of the diagnosis in published work on acalculous biliary disease has relied heavily on the histological finding of chronic cholecystitis on examination of the resected gallbladder. Mackey[40] commented that the histological changes bear little relation to outcome and the use of histology is given perspective by the findings of Carman *et al.*[56]. In a post-mortem review of 5000 unselected patients they found only 17 gallbladders which could be described as histologically normal.

The source of acalculous pain is not known. Motility disorders have been implicated and until recently attention has centred on the gallbladder. The role of the sphincter of Oddi in biliary physiology is increasingly recognized and although sphincter motility may cause post-cholecystectomy symptoms[57,58] the part played by the sphincter in acalculous disease is not known.

Patients suffering from these symptoms often complain bitterly and demand some form of action. In addition the recognition that some serious pathology could mimic biliary disease may lower the surgeon's threshold for laparotomy It is attractive to think that there might be some method of selecting those patients who were likely to benefit from surgery. The intravenous administration of CCK has been suggested as such a method and has been proposed as a useful test to detect those patients whose symptoms will improve following cholecystectomy[18,48–51,59–65].

CCK and gallbladder imaging

Recent work on acalculous biliary disease has employed CCK administration alone as a bedside test without imaging of the gallbladder[48]. In this situation reproduction of the patients' symptoms, particularly pain, within 10 min of CCK administration is regarded as a positive test It has been

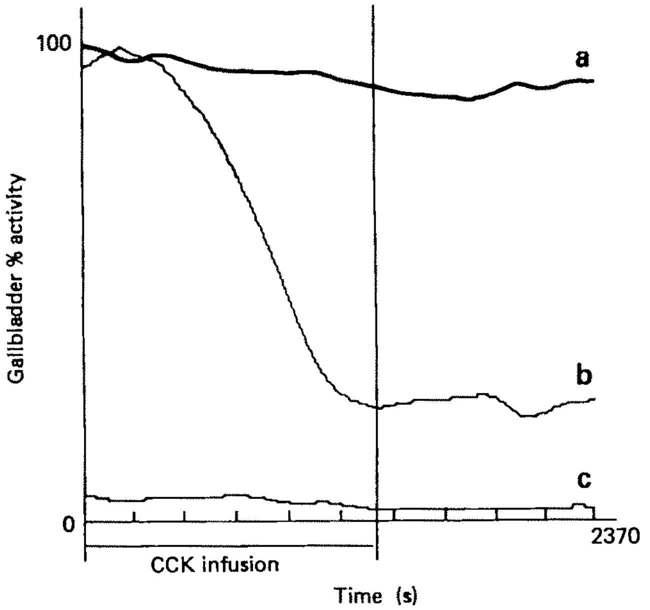

Figure 2 *Derived activity from dynamic scintiscanning of two gallbladders. If the gallbladder is selected as a region of interest the counts/s within that region can be displayed graphically over the period of cholecystokinin (CCK) infusion. The upper curve* (**a**) *is from a patient with a virtually non-responding gallbladder. The ejection half-life is 120 min and the total ejection fraction is 12 per cent. The middle curve* (**b**) *was obtained from a normal volunteer and shows an ejection half-life of 10 min and a total ejection fraction of 65 per cent. The lowermost curve* (**c**) *represents the background activity which is subtracted from the gallbladder activity*

suggested that the pain induced by CCK parallels the onset of gallbladder contraction[63] but Dunn *et al.*[19] and others[18,60] who have imaged the gallbladder during CCK administration noted that pain and reproduction of symptoms are not always related to gallbladder emptying. This might be interpreted as support for an extra-biliary explanation of the pain and suggests that the pain may not be due solely to gallbladder contraction. If gallbladder contraction is the aim of CCK administration it seems sensible to confirm this is actually achieved.

Early studies relied on the use of X-ray films and fluoroscopy to detect gallbladder contraction but these techniques are principally qualitative in nature. Ultrasonography[7-9] and ^{99m}Tc-Sn-2,6-diethylacetylanilidoiminodiacetate (Tc-HIDA) scanning[13,20,66] have allowed quantitative interpretation of gallbladder emptying in response to CCK (*Figure 2*). Attempts have been made to use these techniques to refine identification of patients with acalculous gallbladder disease[20,67] and to predict those who will benefit from surgery. Published results have been encouraging but operation has been performed in small numbers of patients with a relatively short follow-up. More controlled data with longer follow-up is required before the value of these methods can be properly assessed.

CCK and outcome from cholecystectomy

Clinical reports of the value of CCK in practice initially highlighted its use in the identification of patients suspected of having pathologically narrow cystic ducts[50,62,64,65]. Subsequently a series of reports on small numbers of patients suggested that intravenous CCK combined with cineradiography of the opacified gallbladder was useful in selecting symptomatic patients without gallstones who would benefit from cholecystectomy[49,60,61,63]. A test was positive when abnormalities of gallbladder contraction were demonstrated. In addition the reproduction of symptoms was regarded as a basis for a positive test even in the face of normal gallbladder contraction.

Nathan and his colleagues[18] using CCK obtained from the Karolinska Institute reported in 1970 on the combined results of two series of CCK cholecystograms. A total of 141 patients with biliary symptoms but no demonstrable gallstones and 142 normal controls were examined. Each subject received 75 IDU intravenously over 15–30 s. In the patient group, 57 per cent developed pain after injection of CCK and of these two-thirds had reproduction of their symptoms. Of the normal controls, 10 per cent developed pain. Cholecystectomy was performed in 79 patients who were considered positive. The diagnosis was 'confirmed' in 77 patients by microscopy with the minimal requirements for cholecystitis defined as coarse mucosal folds and leucocyte infiltration associated with a degree of fibrosis. Follow-up of 70 of these patients showed substantial improvement in 94 per cent. Eight patients with normal gallbladder emptying and no pain on CCK injection had cholecystectomy. The indications for surgery and outcome in these patients are not clear although six were classified as false negatives when histology showed the changes of chronic cholecystitis. Nathan's group was of the opinion that CCK cholecystography was of value in detecting patients who would benefit from cholecystectomy.

Dunn and his co-workers[19] in 1974 performed CCK cholecystography in 79 patients who had normal oral cholecystograms despite typical gallbladder pain, and in 44 normal volunteers. It was their view that previous studies had unacceptable bias in the interpretation of CCK cholecystograms. In this study three independent radiologists reported the cholecystograms 'blind' and the findings were related to the patients' ultimate outcome. The CCK preparation was the same as in Nathan's study although the 75 IDU dose was given over 45 s. The patient group was arbitrarily divided into two groups. In one group of 44 patients with intermittent pain, labelled as biliary colic, 65 per cent developed pain with CCK. In the group whose pain was continuous, described as 'dyspepsia', significantly fewer (44 per cent) had their pain reproduced by intravenous CCK. Of the 44 normal volunteers 12 developed pain consistent with biliary colic on administration of the CCK which was not significantly different from those labelled as dyspepsia. Twenty-nine patients came to cholecystectomy because of continuation of their symptoms and two were found to have small gallstones on opening the gallbladder. Symptoms were reproduced by CCK in 20 of the 29 patients although the CCK cholecystogram was reported as normal in 11 cases. In the group of nine patients which experienced no symptoms with CCK, three were thought to have abnormal gallbladder contractions on cholecystography. Chronic cholecystitis was found in the majority of gallbladders examined and only two from the positive group and two from the negative group were considered normal. After cholecystectomy 17 of the 20 patients whose symptoms were reproduced by CCK and 6 of the 9 patients who did not respond to CCK were improved. Dunn and his colleagues concluded from this study that CCK cholecystography was not valuable in identifying those patients who would improve after cholecystectomy.

In 1984 Lennard and his co-workers[48] published the results of a series of 42 patients in whom they performed CCK provocation without imaging of the gallbladder. The Kabi-Vitrum preparation was used in a dose of 1 IDU/kg given over 5 min. A placebo injection of normal saline was also used as a control. In this study the patients' pain was given a numerical score using a pain questionnaire. The pain before CCK was compared specifically with the pain experienced during a positive test. If there was no difference between the two scores cholecystectomy was performed. There was no difference in pretest scores between patients who developed pain with CCK and those who did not. All of the 26 patients offered surgery showed improvement with resolution of symptoms. Of the 16 patients with a negative CCK test, 10 were shown to have alternative disorders to explain their symptoms. Of the remaining six patients, five improved spontaneously. These workers were strongly in favour of the CCK test and advocated its use in any patient with persisting pain and negative upper gastrointestinal investigations.

Although the CCK test has appeared to show good discrimination in some papers, an almost universal finding in papers which support the prognostic ability of CCK provocation is that patients with negative tests have not been operated on[18,48,49,51,60–64]. Selection for surgery has been based mainly on the results of CCK provocation on the assumption that this identifies biliary pathology. Those authors who have operated on CCK negative patients on the basis of continued symptoms have failed to show any difference in outcome between CCK positive and CCK negative patients and have not felt CCK provocation to be a useful aid to clinical practice[19,68–70].

Byrne and his colleagues[71] have performed recently a prospective study using a bolus dose of Pancreozymin (1 IDU/kg in 90 s) during cholecystography. They examined 48 patients with a typical history of biliary pain and negative ultrasound and conventional cholecystography. Cholecystectomy was performed in 24 patients. At a mean follow-up of 3 years they have shown no difference in outcome between patients who had radiological abnormalities or symptom reproduction with CCK and those with normal tests. They have further shown no difference in outcome between patients who had cholecystectomy and those managed conservatively.

Our experience of the CCK test in patients thought to have alcaculous biliary pain has been similarly negative[72]. Using a 20 min infusion of Pancreozymin (0.05 IDU/kg per min) we have confirmed gallbladder contraction by Tc-HIDA scanning in each of 64 patients studied. Cholecystectomy has been performed in 26 patients on the basis of continued symptoms and to date we have been unable to show a difference in outcome between positive and negative responders.

Future management of acalculous biliary pain

There is a lack of unequivocal evidence to support the prognostic ability of CCK. The withdrawal of inexpensive preparations leaves no place for the use of CCK as a blind provocative test in the management of patients thought to have acalculous biliary pain. A suggested plan of management for these patients is shown in *Figure 3*. Having established from the patients' history that their pain is consistent with a biliary origin it is important to exclude positively any alternative upper gastrointestinal pathology. This is usually achieved by barium meal or endoscopy. Careful questioning regarding the symptoms associated with irritable bowel syndrome should be carried out[33,47] If a sufficient number of symptoms is present a trial of appropriate diet and antispasmodics may clarify the situation and can occasionally lead to symptomatic improvement.

Only dynamic tests of gallbladder function can demonstrate the existence of gallbladder motility disorders and these relatively non-invasive procedures (ultrasound or Tc-HIDA

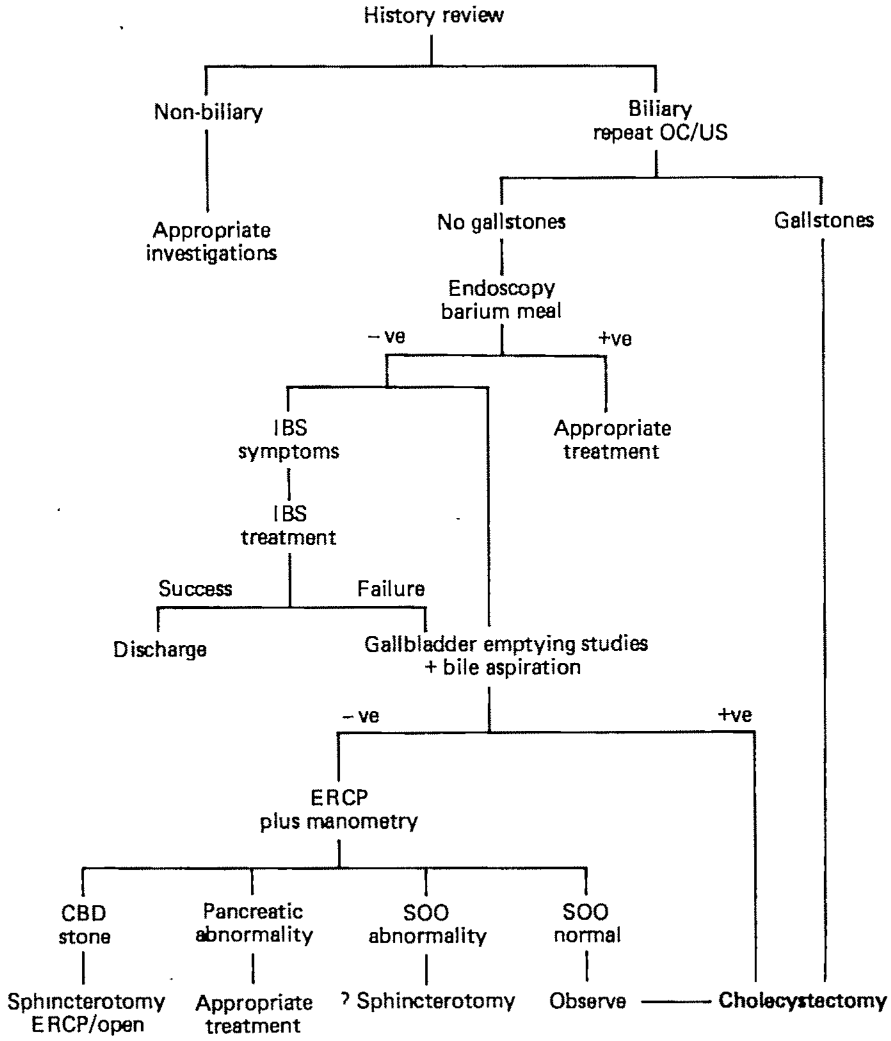

Figure 3 *One possible scheme of management of patients with symptoms suggestive of biliary disease in whom ultrasonography and oral cholecystography are reported as normal US, ultrasonography, OC, oral cholecystography, IBS, irritable bowel syndrome, GB, gallbladder, ERCP, endoscopic retrograde cholangiopancreatography, CBD, common bile duct, and SOO, sphincter of Oddi*

scanning during gallbladder contraction) should be performed next. If CCK is used to contract the gallbladder it must be given by low dose infusion or intramuscular injection. Rapid bolus injections can undoubtedly cause spasm and abnormal contraction even in normal gallbladders and could result in falsely positive results[19,22,23]. Abnormalities found on examination of bile aspirated from the duodenum after gallbladder contraction may be of value although we have no practical experience of such techniques. The absence of such abnormalities on a single examination however cannot exclude a biliary disorder.

There is evidence that sphincter of Oddi motility disorders can lead to biliary pain[57,73]. These abnormalities have been identified principally in postcholecystectomy patients[27,28] and their role in acalculous biliary pain before cholecystectomy is not clear. When gallbladder contraction is shown to be normal the patient must be considered for endoscopic retrograde cholangiopancreatography to exclude common bile duct and pancreatic pathology and to assess sphincter of Oddi function. The presence of a sphincter motility disturbance must be excluded before cholecystectomy as loss of the biliary reservoir may only exacerbate the situation[74,75].

A small number of patients may remain undiagnosed after these investigations. Laparotomy remains the final court of appeal in this situation. Having gone to surgery few surgeons will not perform cholecystectomy and few pathologists will not support a diagnosis of mild chronic cholecystitis. The placebo effect of cholecystectomy must not be underestimated in examining reports of this condition. Many favourable short-term results will deteriorate with longer follow-up[71]. 'Pain of apparently biliary origin remains a real clinical problem with many potential causes. There is confusion within the reported series and controlled clinical studies are lacking. Cholecystectomy as a treatment for this condition retains a limited role but the CCK provocation test has not been proven in clinical practice. We have found planned investigation along the lines suggested in *Figure 3* to be useful in identification and management of the various disorders which can present under this banner diagnosis.

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Role of duodenal bile crystal analysis in the investigation of 'idiopathic' pancreatitis

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Duodenal bile crystal analysis for the detection of gallstones was assessed in 26 patients with acute pancreatitis of known aetiology (11 attributable to gallstones and 15 to alcohol) and in 37 patients without a history of acute pancreatitis (21 with gallstones and 16 without). The sensitivity was 64–67 per cent and the specificity was 94–100 per cent in these groups. Analysis of duodenal bile from 14 patients with 'idiopathic' pancreatitis revealed calcium bilirubinate crystals (but not cholesterol crystals) in 5 patients (36 per cent). Gallstones were confirmed at cholecystectomy in three of these patients and also in one other patient who had a gallstone on a 'late' ultrasound examination but was negative for crystals. Thus 29 per cent of the original 'idiopathic' group had gallstones confirmed. Gallstone analysis showed that pigment stones were present in 7 of 31 (23 per cent) non-pancreatitis controls compared with 9 of 13 (69 per cent) pancreatitis patients (P=0·0048). These results suggest that duodenal bile crystal analysis (involving both calcium bilirubinate and cholesterol crystals) may be a useful technique for the investigation of patients with 'idiopathic' pancreatitis.

Keywords: Cholelithiasis, acute pancreatitis, calcium bilirubinate, cholesterol monohydrate, crystals, bile, gallstone composition

The commonest cause of acute pancreatitis in Great Britain is gallstones[1–5]. Approximately 80 per cent of cases may be detected by ultrasonography (US) and/or oral cholecystography after resolution of the attack[4–6]. Another 10 per cent or so may be detected by endoscopic retrograde cholangiopancreatography (ERCP)[4,7], but the remainder are found only at laparotomy or post-mortem examination[1,4,6,8]. The incidence of 'idiopathic' pancreatitis shows a wide variation, ranging from 9 per cent to 39 per cent[1–5]. Several studies, particularly those of Freund *et al.*[9] and Mayer and McMahon[10], have shown that a significant proportion of those with 'idiopathic' pancreatitis actually have gallstones. Although faecal sieving for gallstones during an attack of acute pancreatitis can increase the detection rate of patients with gallstones[10], it is not at all practical for routine use, nor is it likely to be sufficiently sensitive for the detection of microlithiasis[9,11,12].

The study described here was undertaken to assess the diagnostic role of crystal analysis of bile obtained duodenoscopically after gallbladder stimulation in patients with 'idiopathic' pancreatitis. As a corollary we also analysed the gallstone types found in patients with gallstone pancreatitis.

Patients and methods

Patients

Five groups of patients (total = 77) presenting to Leicester hospitals underwent duodenal bile collection over an 18-month period. The first group consisted of 21 gallstone control patients without a history of acute pancreatitis; 14 were women and 7 were men with a median age of 60 years (range 31–78 years). The second group consisted of 11 women and 5 men without gallstones or a history of pancreatitis; the median age was 54 years (range 30–88 years). The third group consisted of eight women and three men with gallstone-associated pancreatitis; the median age was 71 years (range 32–84 years). The fourth group consisted of three women and twelve men with alcoholic acute pancreatitis and no gallstones, the median age was 47 years (range 36–64 years) The fifth group consisted of five women and nine men initially diagnosed as having idiopathic acute pancreatitis; the median age was 71 years (range 40–94 years).

The diagnosis of gallstones was based on the unequivocal findings at ultrasonography (US), oral cholecystography or ERCP and confirmed at laparotomy where possible The diagnosis of acute pancreatitis was based on a presentation serum amylase >1000 units/l (Phadebas method) in the presence of a compatible clinical picture. The diagnosis of idiopathic pancreatitis was based on the initial set of investigations undertaken within 3 months of an attack of acute pancreatitis; this included at least three US examinations and an ERCP. Patients with hyperlipidaemic disorders and those taking drugs implicated in acute pancreatitis were excluded

All patients with idiopathic pancreatitis underwent 'late' US examination of the gallbladder at the same time as the bile collection These patients were investigated at least 6 months (maximum 36 months) after the attack of acute pancreatitis and were specifically recalled for the purposes of these investigations.

Bile collection

After an overnight fast, patients underwent upper gastrointestinal fibre endoscopy using local analgesia to the pharynx and sedation with 5·0 mg midazolam IV. After aspiration of gastric and duodenal contents, a Wallace sputum collection chamber (No 1514; H. G Wallace Ltd, Colchester, Essex) was connected between the suction tubing of the endoscope and the suction apparatus. With the tip of the endoscope in the second part of the duodenum, 100 units of cholecystokinin-pancreazymin (The Boots Company, PLC, UK) was given IV over 1 min Bile was aspirated over 10–15 min and the collection chamber was then disconnected before withdrawing the endoscope. None of the patients was jaundiced at the time of bile collection.

Bile crystal analysis

Bile samples were centrifuged at 3000 g for 10 min and the sediment examined at 20°C by direct and polarizing microscopy The supernatant was incubated at 37°C for 24 h, re-centrifuged and the new sediment examined. The main types of crystal identified were cholesterol monohydrate and calcium bilirubinate (*Figure 1*). The numbers of crystals were graded 1–4 when present and grade 0 when absent. Grades 1–4 corresponded to the grades specified by Juniper and Burson[13] A positive result (at 20°C, 37°C or both) for cholesterol crystals was taken if graded 1–4 (i.e any crystals present) and for calcium bilirubinate crystals as grades 3 and 4 only (i e. >25 crystals per slide). All bile sample analyses were undertaken by one person (A.F.W) who was unaware of any clinical information.

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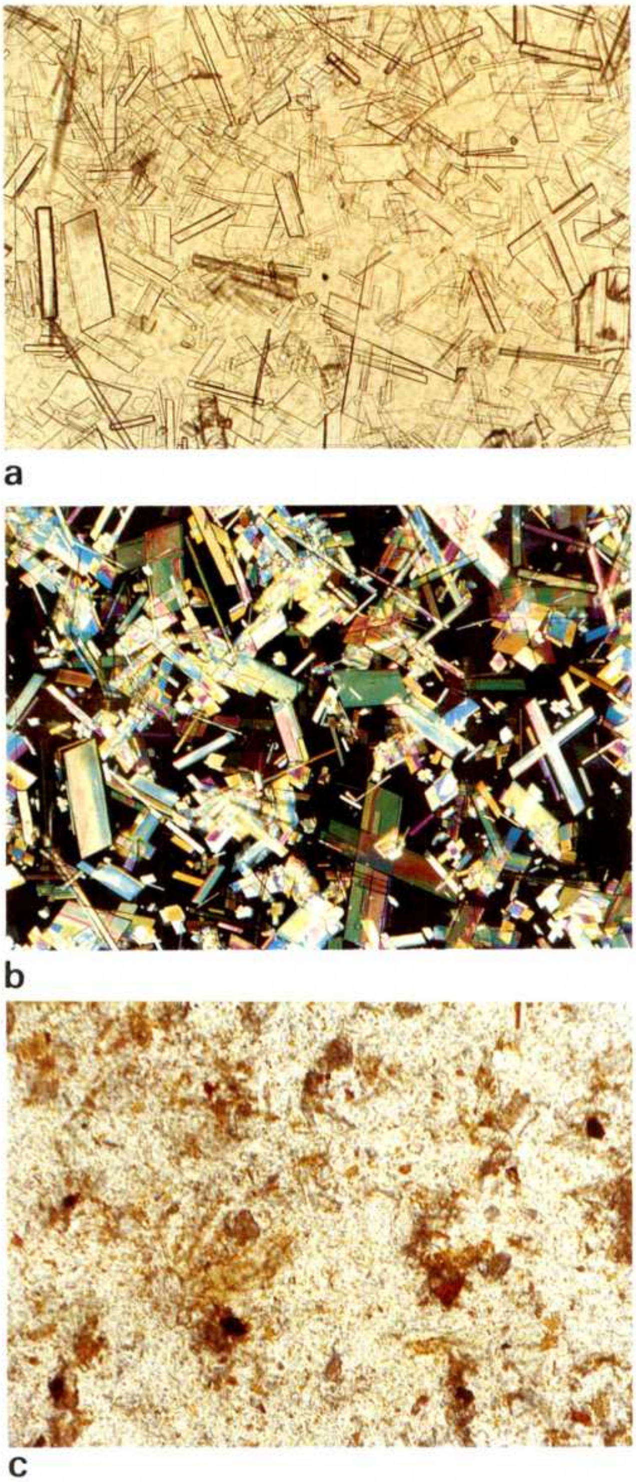

Figure 1 *Cholesterol monohydrate crystals are shown from a patient with cholesterol stones using* **a** *direct and* **b** *polarizing microscopy.* **c** *Calcium bilirubinate crystals can be properly identified, only using polarizing microscopy, as birefringent yellow-brown (almost amorphous) particles. Magnification* ×400

Gallstone analysis

All gallstones were classified into the three main types (cholesterol, calcium bilirubinate and black pigment) by their visual appearance by one person (J.P.N.). Gallstone analysis was undertaken following the method of Ohkubo *et al.*[14]. Washed gallstones were dried over phosphorus pentoxide in a light-protected vacuum desiccator to a constant weight (approximately 4 weeks). The gallstones were cut and both the shell and core (if present) were then analysed separately. Gallstone particles were pulverized using a mortar and pestle and desiccated for another week. Approximately 0·5 mg of powdered gallstone was ground with 100 mg of infrared grade KBr and the mixture re-desiccated for a further 2 weeks. This was made into a thin wafer by compressing in a steel die at 22 000 lb/in^2 for 12 min. The wafer was then analysed using a Perkin-Elmer 598 infrared spectrophotometer. The traces obtained for the three main types of gallstone were very similar to those previously described[14]. The traces for cholesterol gallstones and calcium bilirubinate gallstones were almost identical to traces of pure cholesterol (provided by Alan Hofmann, San Diego, California, USA) and calcium bilirubinate (Sigma UK Ltd, Poole, UK). Mixed cholesterol stones were those that contained at least 50 per cent cholesterol but also a variable amount of calcium bilirubinate either in the shell or core. Pure black pigment stones corresponded to the class A group as defined by Ohkubo *et al.*[14]; those with carbonate corresponded to class C black pigment stones.

Statistical analysis was undertaken using the χ^2 test with Yates' correction.

The study was approved by the Ethical Committee of the Leicester Area Health Authority.

Results

The results of bile crystal analysis in the gallstone and non-gallstone controls are shown in *Table 1* and in the pancreatitis controls are shown in *Table 2*. Nine of the patients with gallstone pancreatitis and all twenty-one gallstone control patients underwent cholecystectomy; gallstones were confirmed in each case.

None of the 14 patients in the idiopathic group had bile cholesterol crystals. One patient had significant calcium bilirubinate crystals at 20°C and another four patients were positive for calcium bilirubinate crystals at 37°C. All 14 patients had (by definition) normal US examinations and 12 had normal ERCP examinations; 2 patients failed ERCP, 1 because of prolonged duodenal obstruction from severe pancreatitis, and the other because of a Polya gastrectomy. Repeat ('late') US examinations revealed single gallstones in three patients, of whom two were positive for crystals; the other patient had a negative bile crystal analysis. The latter and three of those with positive crystal analysis (aged 65–80 years) were subjected to cholecystectomy and gallstones were confirmed (see *Figure 2*). The remaining two patients who were positive for crystals were not subjected to cholecystectomy because they were unfit for surgery.

The results of gallstone analysis are shown in *Table 3*. The

Table 1 *Results of bile crystal analysis in gallstone and non-gallstone controls*

	Gallstone controls ($n=21$)			Non-gallstone controls ($n=16$)		
	Bile crystal analysis			Bile crystal analysis		
Crystal types	20°C	37°C	Both	20°C	37°C	Both
Cholesterol monohydrate	5	2	14	0	0	1
Calcium bilirubinate	0	4		0	1	
Both	6	3		0	0	
None	10	12	7	16	15	15
	Sensitivity = 67%			Specificity = 94%		

Table 2 *Results of bile crystal analysis in patients with gallstone-associated and alcohol-associated acute pancreatitis*

	Gallstone pancreatitis ($n=11$)			Alcoholic pancreatitis ($n=15$)		
	Bile crystal analysis			Bile crystal analysis		
Crystal types	20°C	37°C	Both	20°C	37°C	Both
Cholesterol monohydrate	2	1	7	0	0	0
Calcium bilirubinate	0	1		0	0	
Both	3	2		0	0	
None	6	7	4	15	15	15
	Sensitivity = 64%			Specificity = 100%		

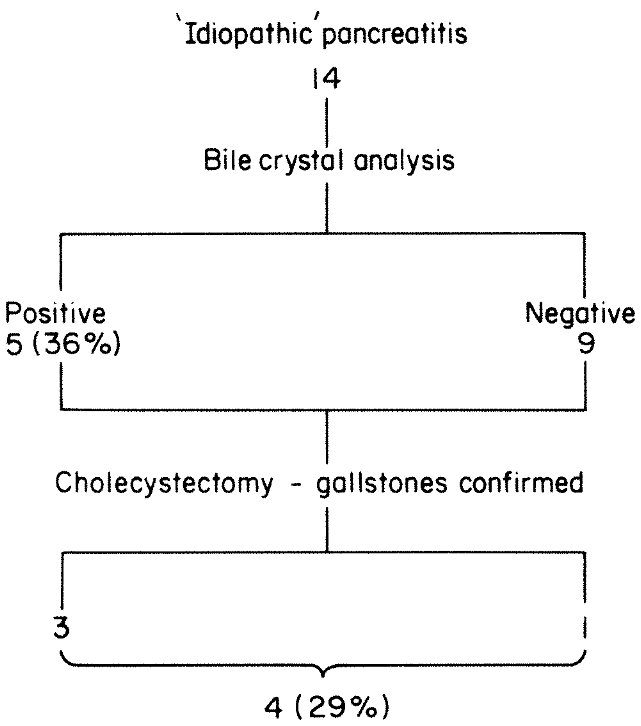
'Idiopathic' pancreatitis
14
Bile crystal analysis
Positive
5 (36%)
Negative
9
Cholecystectomy - gallstones confirmed
3
1
4 (29%)

Figure 2 *Results of bile crystal analysis and gallstone confirmation in 14 patients with 'idiopathic' pancreatitis*

analysis includes gallstones obtained during the study period from 10 patients without pancreatitis who did not have duodenal bile collection. Gallstone types were correct by visual appearance in 40 out of the 44 patients (91 per cent). Stones from 1 of 28 patients with cholesterol stones were misinterpreted as being black pigment stones; stones from 1 of 6 patients with calcium bilirubinate stones were misinterpreted as (mixed) cholesterol stones; stones from 2 out of 10 patients with black pigment stones were misinterpreted as calcium bilirubinate stones.

Whereas cholesterol stones were found in 77 per cent of patients without pancreatitis, these were found in only 31 per cent of those with biliary pancreatitis (χ^2 with Yates' correction = 6·72, d.f. = 1, $P = 0·0048$). The patients with 'idiopathic' pancreatitis had single small stones (approximately 0·5 cm); two had calcium bilirubinate stones and two had black pigment stones.

Discussion

Duodenal bile collection for crystal analysis was first described by Lyon in 1919 (reference 15) and the technique has had limited use since[13,16–22]. Many of these studies, however, have been poorly controlled and the results are often difficult to interpret. There is, nevertheless, a sound theoretical basis for the use of this technique. Bile obtained by gallbladder aspiration at surgery is found to contain cholesterol monohydrate crystals in 92–100 per cent of cases with cholesterol stones, compared with 14 per cent of those with pigment stones[23,24]. Although duodenal gallbladder bile is often supersaturated with cholesterol in subjects without gallstones[23,25] cholesterol crystals are found only in the presence of gallstones[23,26]. This is because cholesterol supersaturation is only one of the factors implicated in gallstone formation; both nucleation and antinucleation factors have also been implicated[27,28]. Single samples of duodenal bile reveal cholesterol crystals in 25–63 per cent of patients with known gallstones[23,26,29]. The sensitivity is increased by incubating bile at 37°C for 24 h or longer and by including calcium bilirubinate crystals in the assessment[23,26,30]. In preliminary studies we found cholesterol and/or calcium bilirubinate crystallization in bile from normal subjects if incubated for 48 h or longer; this has also been demonstrated by others[31]. Marks and Bonorris[26] found that cholesterol crystals occurred intermittently in duodenal bile; by taking samples on three separate occasions and incubating for 48 h, the sensitivity was increased from 25 per cent to 75 per cent.

In the study described here we found that duodenal bile crystal analysis had a sensitivity of 65 per cent and a specificity of 94–100 per cent in patients with and without acute pancreatitis. Moreover, we found that five of the fourteen patients (36 per cent), initially diagnosed as having idiopathic pancreatitis, were positive for crystals. Block and Priest in 1967[32] reported six patients with acute pancreatitis and normal oral cholecystography who had duodenal bile crystals (cholesterol and/or bilirubinate) and gallstones confirmed at laparotomy. Negro *et al.*[33] recently reported cholesterol crystals in three patients with acute pancreatitis and negative ultrasonography, two of whom had microcalculi (< 2 mm) and the other cholesterolosis at cholecystectomy. Our findings are consistent with these results; moreover, unlike those authors, we have also included control patients.

Surprisingly, we found that patients with acute pancreatitis had gallbladder stones which were predominantly of the pigmented varieties. On the other hand, 77 per cent of our non-pancreatitis patients had cholesterol gallstones which is in agreement with series from North America[34,35], Ireland[36] and Australia[37]. We could find no other study, however, which has specifically examined gallbladder stone composition in patients with acute pancreatitis for comparison. The gallstones obtained from the 'idiopathic' pancreatitis patients were all pigment stones. Our number of patients was too small to enable us to conclude whether patients with gallstone pancreatitis tend to form pigment stones *ab initio*, or whether these are formed consequent upon the attack. It is quite feasible that in some patients all the stones are passed into the duodenum during, or soon after, the attack of pancreatitis, only to re-form later. This may explain the initial negative US examinations becoming positive after an interval of several months or more. Unlike cholesterol stones, pigment stones are associated with excess β-glucuronidase activity derived either from the epithelial cells of the hepatobiliary system or from bile bacteria[38]. Whether patients with gallstone pancreatitis have increased bile β-glucuronidase activity remains to be established.

The relatively high incidence of pigment stones in the pancreatitis group emphasizes the importance of including calcium bilirubinate crystal analysis in the assessment, even though this was the only reason for a false positive result in one of the control groups. Indeed, all five patients who were positive for crystals in the 'idiopathic' pancreatitis group had calcium bilirubinate crystals only. Of further interest is that three of the patients had gallstones revealed by 'late' US examination of the gallbladder despite their initial exclusion by exhaustive radiological investigation. This would indicate that repeat US examinations at, say, annual intervals, might be of additional value in this group of patients. The extent to which duodenal bile crystals become apparent before US evidence of gallstones is currently under investigation.

Table 3 *Results of gallstone analysis in patients with and without acute pancreatitis*

Gallstone analysis	Acute pancreatitis ($n = 13$)		Non-pancreatitis ($n = 31$)	
Pure cholesterol	2	cholesterol stones = 4	16	cholesterol stones = 24
Mixed cholesterol	2		7	
Mixed cholesterol with phosphate	0		1	
Calcium bilirubinate	4	pigment stones = 9	2	pigment stones = 7
Black pigment	3		3	
Black pigment with carbonate	2		2	

Despite the relatively low sensitivity of duodenal bile crystal analysis, the high specificity and ease of performance should encourage further independent assessment of the diagnostic usefulness of this technique. This study suggests that its application to patients with 'idiopathic' pancreatitis should produce a good diagnostic yield.

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Sphincter of Oddi dysfunction: results of treatment by endoscopic sphincterotomy

From a consecutive series of 451 patients with post-cholecystectomy symptoms referred for endoscopic retrograde cholangiopancreatography (ERCP), 40 (9 per cent) were diagnosed as having sphincter of Oddi dysfunction. Eight patients were excluded from the study because of incomplete data ($n=6$) *or additional diagnoses* ($n=2$)*. Thirty of the patients had successful ERCP and endoscopic sphincterotomy (ES); this failed in the remaining two because of severe papillary stenosis (6·3 per cent). Endoscopic biliary manometry was performed in 23 patients (77 per cent). Immediate post-ES complications occurred in eight patients (25 per cent). At a median follow-up of 46 months (range 10–88 months) 19 patients had a good outcome (63·3 per cent) and 11 patients had a poor outcome (36·7 per cent). Patients with a good outcome tended to have a delay of months or years following cholecystectomy before the development of symptoms (median 6 years* versus *0 years,* $P=0{\cdot}0003$)*. At ERCP, patients with a good outcome had greater common bile duct diameters (mean ± s.d. mm, 12·6 ± 3·6* versus *8·8 ± 1·8,* $P=0{\cdot}0003$) *and delayed drainage from the biliary tree of injected contrast (13* versus *2 patients,* $P=0{\cdot}02$)*. Endoscopic biliary manometry was abnormal in all 15 patients with a good outcome in whom it was performed but in only 3 out of 8 patients with a poor outcome* ($P=0{\cdot}003$)*. Sphincter of Oddi dysfunction is an important, albeit uncommon, cause of post-cholecystectomy symptoms. ES provides symptomatic relief in the majority of patients but improved criteria for predicting outcome are required.*

Keywords: Sphincter of Oddi, papillary stenosis, dyskinesia, endoscopic retrograde cholangiopancreatography

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Symptoms of abdominal pain or discomfort after cholecystectomy may occur in up to 40 per cent of patients[1–4]. The term 'post-cholecystectomy syndrome' is often used to describe these symptoms but the causes are frequently of non-biliary origin, e.g. peptic ulcer, hiatus hernia, diverticular disease and irritable bowel syndrome. Endoscopic retrograde cholangiopancreatography (ERCP) is the specific radiological investigation of choice as it frequently reveals retained or recurrent common bile duct (CBD) stones, tumours or strictures of the biliary tree and chronic pancreatitis[3,5–7]; long cystic duct remnants may also be revealed but the relationship to symptoms is imprecise[4,8–10].

There remains a small group of patients, however, whose symptoms may be attributed to functional or organic disease of the sphincter complex of the lower CBD, pancreatic duct and ampulla of Vater[4,11–16]. Common features include recurrent biliary-type symptoms, biochemical abnormalities suggestive of partial or intermittent obstruction of the CBD and/or pancreatic duct and sometimes dilatation of the biliary tree, typical pain on retrograde injection of contrast and delayed emptying of contrast from the biliary tree[13,14,17–23].

Various descriptive terms have been applied to these conditions including papillary stenosis, functional biliary dyskinesia, fibrotic Odditis, sclerosing choledocho-Odditis, choledochal junction stenosis, stenosing papillitis, spastic sphincter of Oddi, stenosis of the sphincter of Oddi and hypertonic Oddi's sphincter dyskinesia[11,12,21,24,25]. The recent application of endoscopic biliary manometry[14,21,23,26–31] and computerized radionuclide biliary scanning (RBS)[25,32,33], as well as ERCP, has helped to provide further insights into this group of ampullary disorders. Although there is no accepted nomenclature we shall use the terms 'sphincter of Oddi stenosis' to indicate organic pathology, 'sphincter of Oddi dyskinesia' to describe the functional disorders, and 'sphincter of Oddi dysfunction' to include both of these.

Despite frequent reports of these conditions from Europe[16,21,25,27,28,34,35], America[8,14,17,22,24,26,32,33,36–39], Israel[31], Australia[23] and Japan[30,40], there are doubts as to whether they exist at all[41,42] and there is virtually no mention of these in the British literature. This paper reports our experience to date of patients with suspected sphincter of Oddi dysfunction, with the aim of assessing prognostic criteria of good outcome following treatment by endoscopic sphincterotomy (ES).

Patients and methods

Patients

Patients with post-cholecystectomy symptoms referred for ERCP during a 6-year period (1980–85 inclusive) in Leicester were identified from a prospectively recorded data base The case notes of patients with a diagnosis of sphincter of Oddi dysfunction were reviewed, in all of whom ES had been attempted. In addition to follow-up information available from the case notes, patients were called back at least 6 months after ES for personal interview by one of two independent assessors who had neither referred the patients initially nor had undertaken ERCP/ES. One patient who could not attend because he had moved out of the region was sent a detailed proforma which was fully completed. Biliary pain was defined as pain originating in the epigastrium and/or right hypochondrium, and radiating to the right side of the abdomen and/or the back, and lasting for at least 30 minutes with each attack. Patients were specifically asked if they were asymptomatic, much improved, minimally improved, the same or worse, following ES On the basis of this, patients were divided into those who had a good outcome, i.e were

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Table 1 *Findings at ERCP in 451 consecutive cases referred for post-cholecystectomy symptoms (1980–84 inclusive)*

Findings at ERCP	Number (Total = 451)	Percentage
Normal	148	33
Common bile duct stones	136	30
Sphincter of Oddi dysfunction	40	9
Incomplete investigations	28	6
Pancreas divisum	27	6
Peptic ulcers	23	5
Tumours	18	4
Chronic pancreatitis	14	3
Common bile duct stricture	9	2
Sump syndrome	8	2

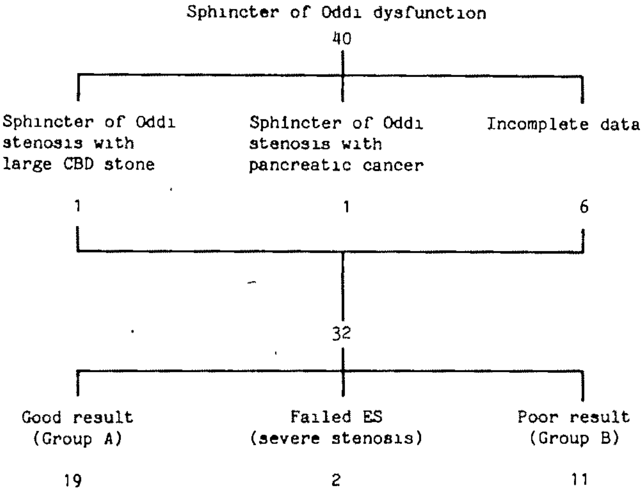
Sphincter of Oddi dysfunction
40
Sphincter of Oddi stenosis with large CBD stone
Sphincter of Oddi stenosis with pancreatic cancer
Incomplete data
1
1
6
32
Good result (Group A)
Failed ES (severe stenosis)
Poor result (Group B)
19
2
11

Figure 1 *Overall outcome in 40 patients who underwent attempted endoscopic sphincterotomy (ES) for suspected sphincter of Oddi dysfunction*

asymptomatic or were much improved following ES (group A), and those who had a poor outcome, i.e. no change, worse or only minimal improvement following ES (group B). The two groups were then compared with respect to clinical history, post-cholecystectomy liver function tests (LFTs), findings at ERCP, and results of manometric studies of the spincter of Oddi.

Endoscopic manometry and ES

Manometry was performed at the same session as, but immediately preceding, ERCP using a triple-lumen catheter with 10 mm spacing of distal openings allowing simultaneous measurement of duodenal, sphincteric and ductal pressures[43] The catheter was passed through the channel of a Fujinon DUOXL or XT duodenoscope and perfused with sterile water at 0·25 ml/min by a pneumohydraulic capillary infusion system (Arndorfer Company, Milwaukee) producing a pressure rise rate of 250 mmHg/s when occluded Ekomatic transducers and a multi-channel brush pen recorder were used to document station pull-through recordings on each patient at least three times during a session and care was taken to avoid administration of any interfering drugs, such that only intravenous diazepam (Valium, Roche) or midazolam (Hypnovel, Roche) were given before manometry. Patients were considered to have abnormal manometry if they were found to have high sphincter of Oddi pressures. On the basis of previous studies[14], manometry was considered to indicate high sphincter of Oddi pressures when baseline values exceeded 40 mmHg above the duodenal reference pressure representing two standard deviations above the mean for a previously studied control group of 22 subjects[44] Endoscopic sphincterotomy was also performed at the same session using a standard technique[45].

Delayed drainage of contrast from the biliary tree was defined as contrast which persisted for more than 45 minutes in the CBD as ascertained by plain abdominal radiographs with the patient in the supine position A dilated CBD was defined as a diameter greater than 10 mm after correcting for magnification

Statistical analysis

Discrete variables were analysed using the χ^2 test and the χ^2 test with Yates' correction for small expected numbers. Continuous variables were analysed using the two-tailed Mann–Whitney U test (Minitab Computer System). Statistical significance was assumed when $P = 0{\cdot}05$, marginal significance was assumed when $P = 0{\cdot}05$–$0{\cdot}10$

Results

There were 451 patients with post-cholecystectomy symptoms who were referred for ERCP during the study period (*Table 1*). Of these, there were 40 patients who had sphincter of Oddi dysfunction (9 per cent), but only 32 patients who had sphincter of Oddi dysfunction as the principal diagnosis and on whom complete data, including follow-up, was obtained (*Figure 1*). A successful ES was achieved in 30 patients of whom 19 (63·3 per cent) had a good outcome (group A) and 11 (36·7 per cent) had a poor outcome (group B). The median follow-up in group A was 44 months (range 10—88 months) and 46 months (range 12–66 months) respectively in group B.

Major clinical features of the two groups are shown in *Table 2* and specific features of the symptomatology (based on history taking) are shown in *Table 3*. The results of the post-cholecystectomy LFTs, findings at ERCP and results of manometry are shown in *Table 4*. All 15 patients in group A who had manometry, had high sphincter of Oddi pressures (> 40 mmHg) compared with only 3 of 8 patients in group B. Twelve patients (63 per cent) in group A had both a dilated CBD and delayed drainage of contrast from the biliary tree compared with none from group B ($P < 0{\cdot}002$). Eighteen (95 per cent) of the patients in group A had a dilated CBD and/or delayed drainage of contrast compared with only two (18 per cent) in group B ($P < 0{\cdot}001$).

Complications of ES occurred in eight patients in whom this was attempted (25 per cent) and ES failed in two because of severe papillary fibrosis (6·3 per cent). These complications were bleeding in three patients, acute pancreatitis in four patients, perforation in two patients and acute cholangitis in one patient Three patients required operation: one had late drainage of a

Table 2 *Important clinical features of the 30 patients who underwent successful endoscopic sphincterotomy for sphincter of Oddi dysfunction*

	Group A ($n = 19$)	Group B ($n = 11$)	P
Female:Male	14.5	11.0	0·001
Age (years)*	57 (34–71)	47 (31–58)	0·0201
Gallstones found at cholecystectomy	19 (100%)	9 (82%)	n.s
Exploration of common bile duct	4 (21%)	†3 (27%)	n.s.
Cholecystectomy to first symptoms (years)*	6 (0–38)	0 (0–4)	0·0003
Symptoms immediately following cholecystectomy	2 (10·5%)	8 (73%)	0·002
First symptoms to endoscopic sphincterotomy (months)*	12 (1–204)	12 (2–72)	n.s.

* Median values (range)· † One patient underwent exploration of the common bile duct at a second admission after cholecystectomy

Table 3 *Type of symptoms in patients with sphincter of Oddi dysfunction before endoscopic sphincterotomy*

Symptoms post-cholecystectomy	Group A ($n = 19$)	Group B ($n = 11$)
Right upper quadrant pain	18 (95%)	11 (100%)
Epigastric pain	3 (16%)	0
Pain radiating into back	1 (5%)	1 (9%)
Fat intolerance	4 (21%)	0
Nausea ± vomiting	2 (11%)	2 (18%)
History of jaundice	8 (42%)	0*
Rigors	2 (11%)	0

* Difference is significant, $P = 0{\cdot}0376$

Table 4 *Potential predictive criteria outcome in the 30 patients who underwent successful endoscopic sphincterotomy for sphincter of Oddi dysfunction*

	Group A ($n=19$)	Group B ($n=11$)	P
γ-glutamyl transpeptidase (units/l)	127 ± 184	61 ± 60	n.s.
Alanine transaminase (units/l)	97 ± 182	301 ± 788	n.s.
Alkaline phosphatase (units/l)	192 ± 191	102 ± 28	n.s
Bilirubin (μmol/l)	14 ± 9	13 ± 9	n.s.
Number of patients with abnormal LFTs	10 (53)	4 (36)	n.s
Number of patients with abnormal LFTs and/or history of jaundice	13 (68)	4 (36)	n.s.
Common bile duct diameter (mm)	12·6 ± 3·6	8·8 ± 1·8	0·0003
Number of patients with common bile duct diameter > 10 mm	16 (84)	0	0·001
Pancreatic duct diameter (mm)	3·2 ± 1·0	3·2 ± 1·1	n.s
Number of patients with pain during cholangiography	6 (32)	8 (73)	0·0734
Number of patients with delayed drainage	13 (68)	2 (18)	0·0232
Number of patients with abnormal manometry	15/15 (100)	3/8 (38)	0·0034

Continuous variables are shown as mean ± s.d. Values in parentheses are percentages

Normal values: γ-glutamyl transpeptidase, 0–50 units/l, alanine transaminase, 2–53 units/l, alkaline phosphatase, 40–130 units/l, bilirubin, 3–17 μmol/l

Table 5 *Details of post-ES symptoms in 10 out of 19 patients with a good outcome—group A. The remaining nine patients became asymptomatic immediately following ES and remained so*

Patient	Age (years)	Sex	Interval of cholecystectomy to symptoms	Post-ES symptoms	Follow-up (months)
1	55	F	2 years	No biliary pain. Other type of pain appeared but relieved by Merbentyl*.	76
2	69	M	2 years	No biliary pain. Vague symptoms for 18 months then asymptomatic.	46 (died MI)
3	69	M	26 years	No biliary pain. Vague symptoms for 36 months then asymptomatic	44
4	43	F	5 years	No biliary pain. Reflux oesophagitis for one month post ES, then asymptomatic after medical treatment.	40
5	62	F	19 years	Asymptomatic for 42 months then developed some symptoms from sigmoid diverticular disease which responded to a high fibre diet	60
6	34	F	3 years	Pain in right loin for 4 months possibly related to renal calculus. Repeat manometry at 6 months showed residual activity. Repeat ES relieved all symptoms	
7	57	M	6 years	No biliary pain. Vague symptoms for 12 months relieved by Merbentyl*, then asymptomatic.	60
8	58	F	5 years	No biliary pain. Vague lower abdominal pain persisted but considerably better overall.	36
9	55	M	Immediate	No biliary pain. Has had three operations for sigmoid diverticular disease, jejunal diverticulosis and incisional hernia	30
10	38	F	Immediate	No biliary pain. Vague lower abdominal pain for 12 months relieved by Merbentyl*, now asymptomatic.	81

* Dicyclomine hydrochloride. MI, myocardial infarct; ES, endoscopic sphincterotomy

post-ES right iliac fossa abscess secondary to perforation; another had drainage of a pseudocyst; the third had a transduodenal sphincteroplasty for bleeding and perforation. There were no deaths in this series.

Ten of the nineteen patients in group A (53 per cent) had a variety of post-ES symptoms and are shown in *Table 5*. Details of the type of symptoms experienced in patients in group B are shown in *Table 6*. Both patients who failed ES because of a markedly scarred papilla have had a poor outcome at 45 and 52 months follow-up. One, a 28-year-old woman, developed stenosis following transduodenal sphincteroplasty and had grossly abnormal LFTs, a CBD diameter of 16 mm and delayed drainage at ERCP; she was asymptomatic for 6 months after a choledochoduodenostomy but the pain subsequently recurred. The other, a 53-year-old woman who had normal LFTs, a CBD diameter of 11 mm and delayed drainage at ERCP, had persisting symptoms but has not undergone surgery.

Discussion

In 1882 Langenbuch suggested that stenosis of the lower CBD could result in pain following cholecystectomy[46]. Florken in 1912 described fibrotic stenosis of the distal CBD[47] and Del Valle and Donovan in 1926 described excellent results for 'papillosphincterotomy' for 'sclerosing choledo-Odditis'[48]. Histological evidence of organic disease of the ampulla has been found in 57 per cent or more of symptomatic patients: although fibrosis is the commonest feature, chronic inflammation, pseudopolyps with granulation and muscular hypertrophy may also be present[12,16,39,49–52]. Although the cause of sphincter of Oddi dysfunction in many patients is stenosis, there still remains a group in whom the histological, surgical or endoscopic features of the ampulla are normal. This group of patients may be considered to have dyskinesia of the sphincter of Oddi[21,30]; dyskinesia ('hypertension') of the pancreatic duct sphincter has also been described[29]. The distinction between stenosis and dyskinesia is not readily made at this juncture and, indeed, they probably overlap. The term sphincter of Oddi dysfunction usefully describes both of these conditions.

The overall incidence of sphincter of Oddi dysfunction in this series of 451 patients was 9 per cent, and compares with values of 6–13·5 per cent reported by three other ERCP studies[34,35,40];

Table 6 *Details of post-ES symptoms in patients with a poor outcome—group B*

Patient	Age (years)	Sex	Interval of cholecystectomy to symptoms	Post-ES symptoms	Follow-up (months)
1	42	F	Immediate	Same symptoms	12
2	58	F	4 years	No change Polysymptomatic—seen by ten different consultants (? Chronic pancreatitis.)	23
3	57	F	Immediate	No change. Belsey MK IV operation for hiatus hernia. Symptoms remained unchanged.	66
4	51	F	Immediate	No change. Repeat ES. Acupuncture and use of nerve stimulator for pain.	64
5	37	F	6 months	No change. Laparotomy for 'adhesions'. Uses hypnosis and relaxation exercises for pain.	53
6	38	F	2 months	Minimal improvement.	46
7*	36	F	2 months	Asymptomatic for 6 months following ES then symptoms recurred. Diagnosed primary hypochondriacal state by psychiatrist.	46
8*	47	F	Immediate	Asymptomatic for 6 months then recurred as before.	
9	49	F	Immediate	Common bile duct exploration following cholecystectomy—'sludge' only found. Worse following ES. Psychiatric referral Known hiatus hernia.	38
10	31	F	Immediate	No change. Numerous hospital admissions for acute pain.	16
11	49	F	Immediate	No change. Psychiatric referral. No help from nerve stimulator for pain	55

* No stones found at cholecystectomy ES, endoscopic sphincterotomy

one series reported an incidence of 19·3 per cent but probably reflects selection[53]. In surgical series of reoperations of the biliary tree post-cholecystectomy, incidences of around 10 per cent have also been reported[10,54], but values of 20–40 per cent are not unusual in Continental Europe[3,55,56]. These discrepancies are partly due to varying degrees of acceptance of sphincter of Oddi dysfunction as a clinical entity, as well as the lack of uniform criteria for diagnosis. The overall prevalence of sphincter of Oddi dysfunction in patients with post-cholecystectomy symptoms is not entirely clear. A manometric study by Bar-Meir *et al.*, involving 454 patients, indicated that only 14 per cent of patients who developed post-cholecystectomy symptoms had sphincter of Oddi dysfunction; this represented less than 0·01 per cent of all post-cholecystectomy patients[31].

Sphincter of Oddi stenosis has been diagnosed at cholecystectomy by failure to pass a Bakes No. 3 dilator or No. 5 ureteric catheter through the lower CBD[8,14,16–19,36,38,50,51,57]. This has not been critically evaluated however; over-enthusiasm for this technique may account for reported incidences of 30 per cent or more for 'papillitis' at cholecystectomy[56]. In the study reported here, in only two patients (6·3 per cent) was it not possible to cannulate the papilla.

Biliary manometry during surgery has also been used as a means of diagnosing organic and/or functional sphincter of Oddi stenosis[3,16,24,37,58,59]. Schuppisser and Tondelli have used cholecystokinin in conjunction with biliary flow manometry and indicated a decreased rate of routine papillotomies from 4·6 per cent to 2·5 per cent for all biliary procedures[16]. Even this figure still seems excessively high when compared with the endoscopic manometric study by Bar-Meir *et al.*[31]. Indeed, Ribeiro and colleagues could find no evidence to support the concept of sphincteric spasm using cholangiomanometry with synchronous cholangiography[42]; as only 86 patients were studied, however, there may have been insufficient numbers to detect this anomaly. Peroperative biliary manometry, combined with fentanyl, has been shown to provide a statistical difference in pressure rise between those with sphincter of Oddi dysfunction and controls[21], but the overlap in values was too great to permit accurate diagnosis. Peroperative sphincter of Oddi manometry has also been employed[39,60] but no firm conclusions can be drawn from the limited studies undertaken.

The morphine–prostigmine or Nardi test has been shown by some studies to be useful both as a screening test for pancreaticobiliary sphincter dysfunction and as a predictor of good outcome following either surgical sphincteroplasty or endoscopic sphincterotomy[22,30,37]. In a recent study involving over 100 subjects, abnormal responses were shown to be more frequent in patients with undefined biliary-type pain and in those with manometrically determined sphincter of Oddi stenosis and dyskinesia[61]. Other studies, however, have indicated that the morphine–prostigmine test cannot reliably detect sphincter of Oddi stenosis or dyskinesia and should not be used as the basis for major clinical decisions[38,62,63]. The morphine–choleretic test may prove to be more reliable but further assessment is required[25]. Warshaw and colleagues have suggested that ultrasound-detected pancreatic duct dilatation during secretin stimulation can be diagnostic of papillary or pancreatic duct stenosis[64], but this work has not been supported by a study from the Middlesex Hospital[65].

On the positive side, computerized radionuclide biliary scanning (RBS) seems to be far more promising as a screening test and perhaps as a diagnostic test[32,33]. Use of RBS without dynamic measurements appears to be less accurate[66,67].

In this study we have diagnosed patients on the basis of biliary-type symptoms in combination with one or more of the other typical features of sphincter of Oddi dyskinesia, namely abnormal LFTs, dilatation of the biliary tree, and delayed emptying of contrast[13,14,17–23]. All of the patients had undergone exhaustive investigations previously to exclude other causes for their symptoms. None of the patients in this series was shown to have an elevated amylase during acute attacks, although some series have included such patients[11,13,22,37,64]. Only 7 of the 30 patients (23 per cent) who had ES had undergone previous surgical exploration of the CBD. This argues against the theory that trauma during choledochotomy is the main factor in promoting sphincter of Oddi stenosis[16]. An alternative explanation advanced by Mallet-Guy in 1945 is that chronic idiopathic dyskinesia may lead to inflammation and ultimately fibrosis[68].

In the study reported here, 19 out of the 30 patients (63 per cent) who had successful ES had a good outcome at follow-up to date. Although good results have been reported in 84–92 per cent of patients from some series[30,53,69], our results are more consistent with the figures of 68 per cent reported by Geenen *et al.*[70] and 61 per cent reported by Roberts-Thompson and Toouli[71]. Studies of surgical sphincteroplasty have indicated good results in 50–97 per cent of patients, but the diagnosis, method of assessing outcome and length of follow-up have often been poorly documented[8,11,12,17,21,22,24,37–39,57,64]. The surgical procedure in some of these patients has also included division and plasty of the pancreatic duct orifice or 'Wirsungotomy'[22,37,39,64].

Patients with a good outcome in this study tended to be older and to give a history of one or more episodes of jaundice. All of the four male patients treated had a good outcome. Only 10 5 per cent of the patients with a good outcome had symptoms immediately after cholecystectomy, compared with 73 per cent of those with a poor outcome. It has been suggested that cholecystectomy allows manifestation of pre-existing symptoms due to sphincter of Oddi dysfunction[15,25]. Gregg *et al.* found that 44 out of 57 patients (77 per cent) with post-cholecystectomy syndrome developed symptoms within 6 months of cholecystectomy, of whom 40 had sphincter of Oddi stenosis diagnosed by ERCP, and suggested that this might be useful pre-operatively[13]. This conclusion is questionable, however, as manometry was not used to corroborate the diagnosis and the effect of treatment was not mentioned[13]. In the present study, patients complaining of debilitating symptoms immediately after cholecystectomy were much more likely to have an extrabiliary functional cause for their symptoms and many were subsequently given a psychiatric diagnosis. Surgical series with good long-term results of 76–88 per cent have also indicated a mean time interval of several years after cholecystectomy before the development of symptoms[21,24,39]

Biliary pain reproduced by injection of contrast was found to be a poor prognostic feature in contrast to a previous report[21]. The presence of a dilated CBD and delayed drainage of contrast following ERCP were both highly predictive of a good outcome. Given adequate selection of patients, these features could be used as a basis for treatment by ES, particularly in cases in whom manometry cannot be adequately achieved because of technical difficulties.

The present study has shown that manometry as a single investigation was the best predictor of a successful long-term outcome. Eighty-three per cent of patients with abnormal manometry had a good outcome, whereas all the patients with normal manometry (five cases) had a poor outcome Geenen and colleagues have reported the results of a prospective randomized study of ES in relation to abnormal basal sphincter of Oddi pressures[70]. Of patients with elevated pressures, 91 per cent were improved by ES, compared with 25 per cent of those with a sham ES; the respective figures for those with normal pressures were 45 per cent and 36 per cent[70]. By contrast, a controlled trial of balloon dilatation of the sphincter of Oddi was unsuccessful in either reducing manometric pressures or improving symptoms, and carried an unacceptable complication rate[72]. As we have previously emphasized, ES performed for sphincter of Oddi dysfunction is associated with a much higher complication rate than uncomplicated choledocholithiasis[45] and may reflect abnormalities of anatomy and vasculature.

In conclusion, sphincter of Oddi dysfunction is an uncommon but real entity. The condition does not appear to be frequent enough to justify routine peroperative sphincter of Oddi manometry at the time of cholecystectomy. The use of a Bakes No. 3 dilator or biliary flow manometry at cholecystectomy to diagnose sphincter of Oddi stenosis and/or dyskinesia cannot be recommended. The morphine–prostigmine test appears to be too idiosyncratic to justify its use as a predictor of outcome following treatment. The patients most likely to benefit from ES are those who develop symptoms at least 6 months after cholecystectomy. The mainstay of diagnosis is endoscopic retrograde manometry, but this is a difficult technique and is not widely available. The success rate for attempted manometry in this series was 77 per cent compared with successes of 54–87 per cent by others[23,31,73]. In pre-selected patients a dilated CBD and delayed emptying of contrast provides a strong presumptive basis for a good outcome following ES. Dynamic RBS requires wider evaluation as a screening test and, indeed, as a diagnostic test.

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Comparison of three Glasgow multifactor prognostic scoring systems in acute pancreatitis

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Modifications have been proposed in an attempt to improve the clinical value of the original nine-factor Glasgow prognostic scoring system for acute pancreatitis. These include the omission of age or serum transaminase, reducing the factors to eight. Debate exists as to which system should be employed. Assessment of the individual factors in 198 attacks of acute pancreatitis treated conventionally revealed that only serum transaminase did not differ significantly between mild and severe outcome groups. Multivariate analysis demonstrated four factors (P_{a,O_2}, white cell count, lactic dehydrogenase, and urea) with independent significance in predicting severity, while serum glucose, albumin and transaminase were least useful. Findings were similar when considering only patients with gallstone aetiology. The reduction of the prognostic factors to eight by the omission of either age or transaminase improved the predictive value of the scoring system, both when considering all attacks and those of gallstone aetiology alone. We suggest that serum transminase should be omitted because: it shows no significant difference between mild and severe outcome groups, while age has prognostic significance; the system has greater sensitivity than if age is omitted; and the number of factors requiring emergency laboratory measurement for immediate prognostication is reduced by one.

Keywords: Acute pancreatitis, multifactor prognostic scoring systems

The original nine-factor Glasgow prognostic scoring system for acute pancreatitis[1] has gained wide acceptance in the UK. Modifications have been proposed in an attempt to improve its clinical value. The omission of age, thereby reducing the number of factors to eight, and an increase in the prognostic threshold for transaminase to 200 units/l, has been suggested in patients with gallstone-associated pancreatitis[2]. These changes were based on a study of 47 patients. Subsequently an appraisal of the original nine prognostic factors in 405 episodes of pancreatitis suggested that transaminase should be omitted in preference to age[3].

This study was designed to elucidate which of these three systems (*Table 1*) is most useful in predicting outcome of pancreatitis in a typical UK population.

Patients and methods

Data have been collected on patients with acute pancreatitis admitted to five hospitals in and around Leicester since 1983. This report is based on 198 attacks of pancreatitis in 172 patients in whom all nine of the original Glasgow prognostic factors were measured within 48 h of admission. Acute pancreatitis was diagnosed when the serum amylase was greater than 1000 units/l using the Phadebas method (normal range 70–300 units/l) with a compatible clinical picture. All attacks were treated conventionally. Patients entered into the treatment limbs of trials of fresh frozen plasma therapy[4] and endoscopic sphincterotomy[5] in acute pancreatitis were excluded.

Age and sex were recorded for each patient. For statistical analysis the highest value recorded within 48 h of admission was used for the serum concentrations of alanine transaminase (ALT), lactate dehydrogenase (LDH), blood glucose and white cell count (WCC) and the lowest concentrations of arterial oxygen saturation (P_{a,O_2}), serum albumin and calcium.

Gallstones were diagnosed by the unequivocal demonstration of calculi by imaging methods (ultrasound, oral cholecystography, endoscopic retrograde cholangiopancreatography) or at subsequent surgery or necropsy. Alcohol abuse was accepted as the aetiological factor when gallstones were excluded and there was a history from the patient or the patient's family of heavy alcohol intake within 4 days of admission or prolonged alcohol abuse.

Table 1 *The three Glasgow multifactor prognostic scoring systems*

Prognostic factors*	Imrie *et al.* (1978)	Osborne *et al.* (1981)	Blamey *et al.* (1984)
Age (years)	>55	Omitted	>55
Serum transaminase (units/l)	>100	>200	Omitted
White cell count (×10^9/l)	>15	>15	>15
Blood glucose (mmol/l)	>10	>10	>10
Serum urea (mmol/l)	>16	>16	>16
Arterial oxygen saturation (kPa)	<8	<8	<8
Serum calcium (mmol/l)	<2	<2	<2
Serum albumin (g/l)	<32	<32	<32
Serum lactate dehydrogenase (units/l)	>600	>600	>600

* 0–2 adverse factors predicts mild disease; 3 or more adverse factors predicts severe disease

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Table 2 *Analysis of the risk factors in terms of severity of clinical outcome for all attacks and gallstone aetiology only**

	All attacks			Gallstone aetiology only		
Prognostic factor	Mild outcome	Severe outcome	$P^{\dagger}$	Mild outcome	Severe outcome	$P^{\dagger}$
Arterial oxygen saturation (kPa)	10·6 (9·2–11·8)	7·65 (7·0–9·2)	0·0001	10·3 (8·7–11·4)	8·0 (7·2–9·3)	0·0003
White cell count (×10^9/l)	13·5 (10·9–16·5)	18·6 (15·7–21·8)	0·0001	14·0 (11·7–17·1)	17·4 (14·0–21·9)	0·0176
Serum urea (mmol/l)	3·2 (4·0–7·0)	9·9 (7·3–14·2)	0·001	5·6 (4·5–7·5)	10·3 (7·5–11·6)	0·0001
Serum lactate dehydrogenase (units/l)	306 (236–420)	457 (320–725)	0·0008	347 (240–431)	363 (268–671)	0·2150
Age (years)	56 (36–72)	71 (53–82)	0·0006	68 (51–76)	76 (60–83)	0·0339
Serum calcium (mmol/l)	2·2 (2·1–2·35)	2·1 (1·8–2·25)	0·0017	2·2 (2·1–2·3)	2·1 (1·7–2·2)	0·0172
Blood glucose (mmol/l)	7·1 (6·2–9·4)	9·2 (7·7–11·1)	0·0013	7·2 (6·1–9·5)	9·2 (7·8–11·3)	0·0052
Serum albumin (g/l)	37 (35–41)	35 (31·5–39)	0·0239	37 (34–40)	35 (32–39)	0·1467
Serum alanine transaminase (units/l)	54 (20–136)	63 (19–196)	0·5828	104 (43–272)	79 (19–261)	0·4366

* Values are given as medians with interquartile ranges in parentheses
† Two-tailed Mann–Whitney ranking test

Table 3 *The clinical value of the three prognostic scoring systems for all attacks and for gallstone aetiology only*

	Imrie *et al* (1978)		Osborne *et al* (1981)		Blamey *et al.* (1984)	
	All attacks	Gallstone only	All attacks	Gallstone only	All attacks	Gallstone only
Sensitivity (%)	85·3	82·4	73·5	64·7	79·4	70·6
Specificity (%)	73·8	63·5	85·4	78·1	79·9	77·1
Prediction correct (%)	75·6	62·8	83·3	76·1	79·8	73·5

The pancreatitis was classified as severe if the patient died or developed a major complication resulting in hospital stay in excess of 20 days, having excluded social problems or elective biliary surgery as reasons for prolonging the admission.

Between-group comparisons were achieved using the two-tailed Mann–Whitney ranking test Multivariate analysis was by stepwise logistic regression[6].

Results

Of the 198 attacks of acute pancreatitis studied in 172 patients, 52 per cent were in women and the median age of the patients was 59 years (range 13–91). The aetiology was gallstones in 57 per cent, alcohol in 21 per cent, other aetiologies in 8 per cent and idiopathic in 14 per cent. Thirty-four attacks (17·2 per cent) were classified as severe and there were 17 deaths (8·6 per cent) in this group of patients. The remaining 164 attacks were classified as mild.

When comparing gallstone-related attacks with non-gallstone attacks, two of the nine prognostic factors (age and ALT) were significantly higher in the gallstone-related attacks ($P < 0·001$). When considering all attacks, eight of the factors showed significant differences between the severe and mild groups (*Table 2*). In this analysis the serum ALT concentration was not useful in predicting severe pancreatitis. When considering only attacks with gallstone aetiology, three factors (LDH, albumin and ALT) showed no significant difference between mild and severe groups (*Table 2*).

Stepwise logistic regression revealed that the factors with independent significance in determining severity for all attacks were P_{a,O_2}, WCC, LDH and urea. The discriminant function (R) generated by this method was:

$$R = +0·387 + 0·202\ \mathrm{WCC} + 0·083\ \mathrm{urea} - 0·744\ P_{a,O_2} + 0·002\ \mathrm{LDH}$$

When these four factors were controlled for, P values of 0·161 and 0·239 respectively were recorded for age and calcium, while glucose, albumin and ALT all had P values $>0·5$.

When looking at the 113 attacks with gallstones as the aetiology, stepwise logistic regression showed that three factors had independent significance in determining severity (P_{a,O_2}, urea and WCC). The discriminant function generated was:

$$R = +1·086 + 0·107\ \mathrm{WCC} + 0·119\ \mathrm{urea} - 0·595\ P_{a,O_2}$$

The sensitivity, specificity and predictive value of the three prognostic scoring systems for all attacks and attacks of gallstone aetiology only is given in *Table 3*.

Discussion

Acute pancreatitis is a disease with a wide spectrum of severity Eighty per cent of attacks are mild with rapid recovery on conservative treatment alone. The remaining 20 per cent of attacks are severe with a protracted course and a mortality rate of 50 per cent.

Williamson[7] suggested three reasons for separating patients into groups with good and bad prognosis on admission:

(1) The severe group need more vigorous resuscitation and monitoring including intensive care facilities, urethral catheterization and central venous monitoring. This would be costly if applied to all patients with acute pancreatitis
(2) Aggressive treatment such as early surgery, peritoneal lavage or endoscopic sphincterotomy might be justified in patients with a poor outlook but not in the majority of patients with a mild attack which will quickly abort.
(3) General acceptance of criteria of severity facilitates international comparisons for prospective studies.

Unfortunately in no other abdominal condition is the outcome so unpredictable at the outset. Differentiation at the time of presentation between mild and fulminating pancreatitis on clinical grounds alone is unreliable. Although patients with severe pancreatitis may arrive in hospital shocked and comatose, they are more likely to appear clinically well on initial assessment, only to deteriorate in the ensuing hours or days. Initial clinical evaluation is successful in identifying only 34–39 per cent of patients with severe disease[8,9]. While this figure does improve to 73 per cent at 24 h and to 83 per cent at 48 h[8,9], there is still a need for supplementary indices of severity However, these are of limited value unless they provide an answer within 48 h of admission.

Biochemical and haematological indicators of the severity of inflammatory response and the degree of multi-organ derangement can be used to supplement clinical judgement in this early phase. Ranson and his colleagues[10–12] found that 11 of 43 clinical biochemical and haematological factors determined within 48 h of admission had prognostic significance in their patients with acute pancreatitis. When used prospectively a scoring system based on these factors identified 162 patients who had less than three factors present, of whom only one proved to have severe disease, while 24 of 38 patients with three or more factors had major complications or died.

Imrie *et al*[1] discarded three of Ranson's factors (fluid sequestration >6 litres, base deficit >4 mmol/l and haematocrit decrease of >10 per cent within 48 h of admission) and introduced serum albumin <32 g/l to provide nine criteria. In addition the criterion aspartate transaminase concentration >250 Sigma Frankel Units per cent was replaced by the criterion that either aspartate transaminase or ALT concentrations exceeded 100 units/l. In their initial report all patients who died were correctly predicted as severe by the scoring criteria.

In Ranson's series pancreatitis was predominantly due to alcohol abuse (69 per cent of 300 patients) and occurred more commonly in men (78 per cent). In the UK biliary disease is the most common aetiological factor (50–60 per cent of cases) and acute pancreatitis occurs more commonly in women[1,8,13,14]. In view of these differences the predictive value of individual factors must be verified within each clinical setting.

Age and serum transaminase have both been shown to predict a gallstone aetiology in acute pancreatitis[14–16] and the prognostic factors may require modification in biliary disease[2,17]. The majority of patients are aged over 55 years and mild transaminase enzyme elevation occurs frequently, with the result that more patients are judged severe on the basis of prognostic factors.

Osborne *et al.*[2] found that in the subgroup of patients with gallstone-associated pancreatitis the factor age >55 years was not of individual prognostic significance. They suggested modification of Imrie's original system to use only eight factors and raising of the threshold for transaminase to 200 units/l. In a much larger series of patients Blamey *et al.*[3] confirmed the predictive value of eight of the nine original factors adopted by Imrie *et al.* Only the transaminase concentration had no significance in predicting the severity of acute pancreatitis. Exclusion of transaminase improved the overall predictive value from 72 per cent to 79 per cent.

The present study confirms an improved prognostic performance for both modifications of the original Glasgow system. Omission of age and increase of the prognostic threshold of transaminase to 200 units/l improved the percentage of correct predictions from 75·6 to 83 3 when considering all attacks and from 62 8 to 76·1 when considering attacks of gallstone aetiology alone[2] Omission of transaminase in preference to age[3] improved the percentage of correct predictions to 79·8 for all attacks and to 73·5 for gallstone attacks There appears to be little to choose between the two modifications, but in Leicester we prefer to omit serum transaminase because it is the only factor showing no significant difference between mild and severe outcome groups when considering all attacks and attacks with a gallstone aetiology alone. Age has prognostic significance in both groups (*Table 2*). In addition the omission of transaminase preserves the sensitivity of the scoring system better than omission of age (*Table 3*) and reduces by one the number of factors requiring laboratory measurement for immediate prognostication. Continuing clinical vigilance is of great importance in the light of the performance of these scoring systems.

Multivariate analysis of risk factors has been used by Ranson and Pasternack[18] for accurate prediction of severity of acute pancreatitis. Minimizing the number of variables by using only those with independent significance may provide an alternative method[3], but this awaits prospective verification. Blamey *et al.*[3] found that LDH and calcium were the only Glasgow criteria with independent significance in determining severity. In the present study four factors (P_{a,O_2}, WCC, LDH and urea) showed independent significance when all attacks were analysed and three factors (P_{a,O_2}, WCC and urea) when considering only attacks of gallstone aetiology.

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Influence of age on the mortality from acute pancreatitis

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The influence of age on the mortality rate of 268 patients with acute pancreatitis was studied. The hospital mortality rate for patients aged below 50 years was 5·9 per cent. The figure increased to 21·3 per cent in patients aged over 75; the high mortality was accounted for by a higher incidence of deaths related to concomitant medical or surgical diseases in the same hospital admission rather than to complications resulting directly from the pathological process of acute pancreatitis. When only deaths due to complications of acute pancreatitis were analysed, the mortality rate was not significantly different between the young and elderly groups. Moreover, the complication rate and the proportion of patients having severe disease (judged by the number of prognostic signs) were not higher in the elderly. Thus acute pancreatitis was intrinsically not more serious were it not for the presence of concomitant diseases with advanced age.

Keywords: Acute pancreatitis, age, mortality

Both the absolute and relative numbers of elderly people in the world have been steadily increasing[1]. Managing the elderly with acute surgical illness may at times be difficult due to concomitant or hidden medical problems. It is generally believed that after surgical procedures, elderly patients do not fare as well as their younger counterparts[2]. Such belief is also extended to acute pancreatitis in which surgery in the acute phase is often not necessary[3–5]. While advanced age was considered by both Imrie *et al.*[6] and Ranson and Pasternack[7] to be one of the many high risk factors, in assessing the severity and prognosis of acute pancreatitis it is more important to predict the risk of death or complication irrespective of the age of the patient[8]. What contributes to the high mortality in elderly patients with pancreatitis has not been thoroughly investigated. We therefore undertook a detailed study on the elderly patients in our practice with the following aims: (1) to verify that mortality in acute pancreatitis does increase with advancing age and (2) to identify factors contributing to the high mortality in the elderly.

Patients and methods

From 1983 to 1986, 268 patients with acute pancreatitis were seen in the Department of Surgery, University of Hong Kong, Queen Mary Hospital Data from these patients were collected prospectively and computerized. The diagnosis of acute pancreatitis was based on a consistent clinical presentation and a serum amylase level above 400 units/l (normal range for our laboratory 25–75 units/l). The patients were initially managed conservatively and emergency operations were performed only when biliary tract infection and/or pancreatic sepsis was suspected. Ultrasonography of the biliary tract, liver and pancreas was done soon after admission Endoscopic retrograde cholangiopancreatography (ERCP) was performed after resolution of pancreatitis. The patients were considered to have recovered from pancreatitis if the abdomen was not tender, intestinal function had resumed and the serum amylase level had returned to normal. Patients who had ultrasonographic evidence of stones in the gallbladder or common bile duct but failed cannulation during ERCP had oral cholecystography or percutaneous transhepatic cholangiography We searched for biliary stones diligently because biliary pancreatitis is more common in our locality[9] Those patients with documented biliary stones were urged to have operations on the nearest elective operation day.

On admission and at 48 h, two sets of haematological and biochemical measurements were performed. The modified prognostic factor scoring system[10] (eight factors, excluding age) was used to grade the severity of the disease. This set of parameters was used because they had been shown to be more appropriate for patients with biliary pancreatitis[10] Moreover, as it was the aim of this study to investigate the influence of age on the outcome of the disease, age was excluded from the grading system.

Local complications (e.g. necrotizing pancreatitis, pancreatic abscess, pseudocyst, duodenal and biliary obstruction) and systemic complications (e.g. respiratory failure, renal failure, cardiogenic shock, gastrointestinal bleeding, disseminated intravascular coagulation) were noted and treated accordingly

Hospital mortality was defined as death within the same hospital admission for the attack of acute pancreatitis.

The χ^2 test (with Yates' correction for cell number less than 10) was used for statistical analysis.

Results

Two hundred and sixty-eight patients were seen. The patients' ages ranged from 14 to 95 years, with a median age of 59 (*Figure 1*). There were 115 men and 153 women.

By means of ultrasonography (204 patients), ERCP (195 patients), percutaneous transhepatic cholangiography (5 patients) and oral cholecystography (36 patients), exactly half of the patients were found to have either gallstones, common duct or intrahepatic duct stones (*Table 1*). Alcohol abuse was the cause of pancreatitis in 33 patients only. One patient was found to have hepatocellular carcinoma; the exact aetiology of pancreatitis in this patient was not certain, but could be the result of transient obstruction of the pancreatic duct due to tumour fragments passing through the ampulla. In 91 patients, the aetiology of acute pancreatitis could not be identified.

Forty-two patients were known to have one or more medical diseases before the onset of pancreatitis: hypertension (15

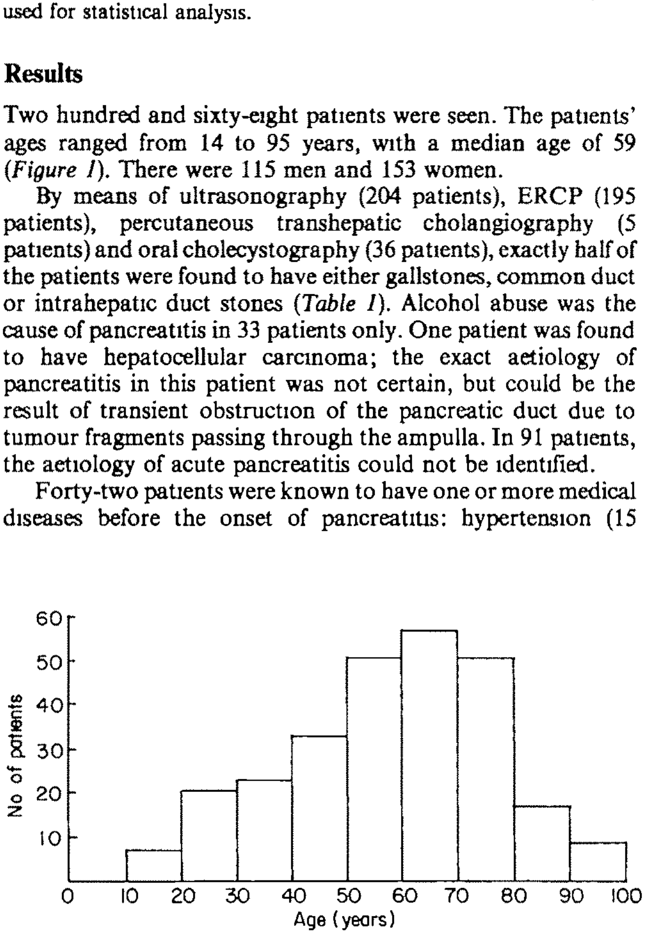

Figure 1 *Histogram of incidence of acute pancreatitis according to age*

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Table 1 *Aetiology of acute pancreatitis*

Alcohol	33
Biliary stone	134
Ascaris in common bile duct	2
Clonorchis in common bile duct	1
Ascaris in pancreatic duct	1
Hepatocellular carcinoma	1
Hyperlipidaemia	2
Hypercalcaemia	1
Mumps	1
Pregnancy	1
Idiopathic	91
Total	268

Table 2 *Complications* and direct causes of hospital mortality in patients with acute pancreatitis*

Complication	No. of patients†
Local	
Necrotizing pancreatitis	13 (11)
Pancreatic pseudocyst	5 (1)
Pancreatic abscess	10 (6)
Duodenal obstruction	1
Biliary obstruction	1
Systemic	
Gastrointestinal bleeding	14 (1)
Renal failure	5
Respiratory failure	11
Disseminated intravascular coagulation	3
Cardiogenic shock	1
Others	
Cholangitis	2 (2)
Cholangitic liver abscess	1 (1)
Myocardial infarction	2 (2)
Dissecting aneurysm	1 (1)
Chronic obstructive airway disease	1 (1)

* 39 patients developed a total of 64 complications
† Numbers in parentheses indicate the number of patients who died of the complication

patients), diabetes mellitus (13 patients), ischaemic heart disease (11 patients), chronic obstructive airway disease (5 patients), liver cirrhosis (3 patients), cerebrovascular accident (2 patients), asthma (2 patients), hyperthyroidism (1 patient), hypothyroidism (1 patient) and uraemia (1 patient). Of these, 37 (88 per cent) were aged over 50.

Thirty-nine patients (14·6 per cent) developed one or more local or systemic complications of acute pancreatitis (*Table 2*). Hospital mortality occurred in 26 patients (9·7 per cent), 19 of whom died from complications as a direct consequence of the pathological process of acute pancreatitis Twelve of these 19 patients had a rapid deteriorating course, and in these cases necropsy demonstrated necrotizing pancreatitis in 11 and pancreatic abscess in 1. Six patients died of septic complications of pancreatic abscesses and infected pseudocyst. One patient died of uncontrolled bleeding from gastric erosions. In the remaining seven, death was not a direct result of the pathological process of pancreatitis. Three of these patients died of complications related to biliary stones (two from cholangitis, one from liver abscess) after the acute pancreatitis had resolved. Two patients died of myocardial infarction. One patient died of dissecting aortic aneurysm and another died of respiratory failure secondary to chronic obstructive airway disease after resolution of the acute pancreatitis.

The severity of the disease assessed by prognostic factor scoring system[10] in relation to the complication and mortality is shown in *Table 3*. Of the 103 patients with disease assessed as severe (with 3 or more prognostic factors), 25 patients (24·3 per cent) developed complications and 19 patients (18·4 per cent) died. When compared with the group assessed as mild, the difference in complication and mortality rate was highly significant (complication rate $\chi^2=12·7$, $P<0·001$; mortality rate $\chi^2=13·0$, $P<0·001$).

We calculated the morbidity and mortality rate in groups of patients with advancing age. The procedure was started with patients above 50 years of age and the rates were compared with the group below 50 years of age. The aetiology and the severity of the disease were compared and graded in each corresponding age group at 5-year intervals in a similar manner.

There was a preponderance of biliary pancreatitis in all age groups above 50 and the incidence increased with age (*Table 4*). The proportion of patients with three or more poor prognostic factors was similar in each elderly group irrespective of the age dividing line and there was no statistically significant difference when the elderly were compared with younger patients (*Table 5*).

The complication rate increased slightly with advancing age (*Table 6*). No statistically significant difference between the groups at each age dividing line was found. However, with advancing age, the incidence of systemic complications increased and that of local complications decreased (*Figure 2*).

The overall hospital mortality rate increased with age. The difference in mortality rate between each corresponding age group was significant from 75 onwards. Above age 75, 21·3 per cent of the patients died. However, if we analysed only the 19 patients who died as a direct consequence of the pathological process of acute pancreatitis, the mortality rate of the elderly patients was then not statistically different from their younger counterparts (*Table 6*).

Only 15·6 per cent of patients were admitted with known medical diseases. The influence of this factor on the mortality rate was also analysed. Twenty (76·9 per cent) of the deceased

Table 3 *Relation between positive prognostic factors[10] and outcome of acute pancreatitis*

No. of prognostic factors	Patient number	Complication ($n=39$)	Mortality ($n=26$)
0	37	5 (13·5%)	1 (2·7%)
1	59	5 (8·5%)	4 (6·8%)
2	69	4 (5·8%)	2 (2·9%)
3	58	12 (20·7%)	8 (13·8%)
4	34	7 (20·6%)	4 (11·8%)
5	8	4 (50·0%)	4 (50·0%)
6	3	2 (66·7%)	3 (100%)

Table 4 *Incidence of biliary stone in different elderly age groups*

Age group	No. of patients	Biliary tract stones	Statistical significance	
			χ^2	P
<50	85	31 (36·5%)	9·11	<0·005
>50	183	103 (56·3%)		
<55	111	45 (40·5%)	6·78	<0·01
>55	157	89 (56·7%)		
<60	136	60 (44·1%)	3·82	0·05
>60	132	74 (56·1%)		
<65	165	68 (41·2%)	13·26	<0·001
>65	103	66 (64·1%)		
<70	193	83 (43·0%)	13·50	<0·001
>70	75	51 (68·0%)		
<75	221	102 (46·2%)	7·46	<0·01
>75	47	32 (68·1%)		
<80	242	114 (47·1%)	8·35	<0·005
>80	26	20 (76·9%)		
Total	268	134		

Table 5 *Grading of severity by prognostic factor scoring*[10]

Age group	No of patients	Patients with ⩾3 factors
<50	85	30 (35·3%)
>50	183	73 (39·9%)
<55	111	42 (37·8%)
>55	157	61 (38·9%)
<60	136	49 (36·0%)
>60	132	54 (40·9%)
<65	165	61 (37·0%)
>65	103	42 (40·8%)
<70	193	75 (38·9%)
>70	75	28 (37·3%)
<75	221	82 (37·1%)
>75	47	21 (44·7%)
<80	242	94 (38·8%)
>80	26	9 (34·6%)
Total	268	103 (38·4%)

Table 6 *Complication and mortality rate of acute pancreatitis in different age groups*

Age group	No. of patients	Complication	Mortality related to acute pancreatitis	Hospital mortality
<50	85	8 (9·4%)	5 (5·9%)	5 (5·9%)
>50	183	31 (16·9%)	14 (7·7%)	21 (11·5%)
<55	111	11 (9·9%)	8 (7·2%)	8 (7·2%)
>55	157	28 (17·8%)	11 (7·0%)	18 (11·5%)
<60	136	15 (11·0%)	9 (6·6%)	9 (6·6%)
>60	132	24 (18·2%)	10 (7·6%)	17 (12·9%)
<65	165	20 (12·1%)	12 (7·3%)	12 (7·3%)
>65	103	19 (18·4%)	7 (6·8%)	14 (13·6%)
<70	193	26 (13·5%)	15 (7·8%)	15 (7·8%)
>70	75	13 (17·3%)	4 (5·3%)	11 (14·7%)
<75	221	28 (12·7%)	14 (6·3%)	16 (7·2%)*
>75	47	11 (23·4%)	5 (10·6%)	10 (21·3%)*
<80	242	32 (13·2%)	17 (7·0%)	20 (8·3%)†
>80	26	7 (26·9%)	2 (7·7%)	6 (23·1)†
Total	268	39 (14·6%)	19 (7·1%)	26 (9·7%)

* $\chi^2=8{\cdot}71$, $P<0{\cdot}025$
† $\chi^2=5{\cdot}88$, $P<0{\cdot}025$

patients did not have a history of medical disease. Overall, this factor did not influence the mortality rate.

Discussion

Acute pancreatitis affects people of all ages. Old people are commonly involved; in the present series, 68·2 per cent of patients were aged over 50. This is not unexpected as biliary tract disease is a more frequent cause of acute pancreatitis in the elderly[11] and the incidence of cholelithiasis increases with age[12].

The mortality from acute pancreatitis did increase with advancing age. When the patients were over 75, the mortality rate was more than double that of the entire series. However, some of the deaths in the elderly in this series were related to complications of biliary stones and other diseases. This could be due to a higher prevalence of cardiopulmonary diseases and biliary stone in the elderly and a preceding attack of acute pancreatitis might have aggravated or precipitated their development. If such concomitant diseases are ignored, then the mortality rate due to acute pancreatitis *per se* was not statistically different between the young and the elderly. Thus acute pancreatitis in the elderly was intrinsically not more serious were it not for the presence of these concomitant diseases. This point was further supported by the finding in this study that the proportion of patients having severe disease on admission and the complication rate were not higher in the elderly.

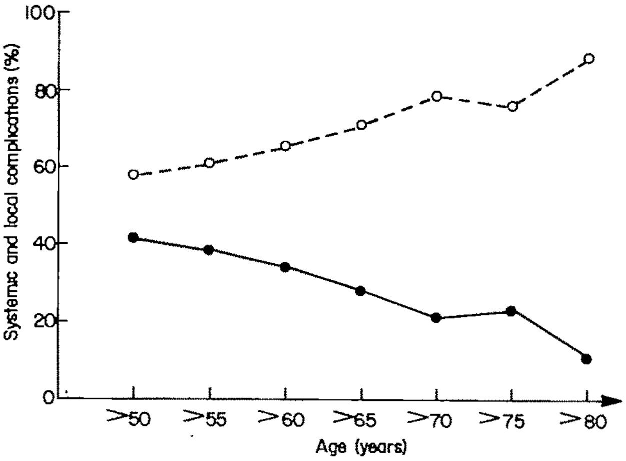

Figure 2 *Incidence of systemic and local complications at advancing age groups.* ○, *Systemic complication,* ●, *local complication*

The pattern of complications changed with age While local complications of acute pancreatitis occurred largely in young patients, the incidence of organ failure increased with age. This phenomenon could be related to the progressive decline in physiological function of major organs with ageing[13,14]. Thus their ability to withstand the stress of acute pancreatitis was reduced and multiple organ failure manifested. It was surprising to find that pre-existing medical diseases did not worsen the prognosis in this series. Such findings accord with those of Trapnell[4] and Park *et al.*[5]. However, the absence of a history of medical disease could not exclude the possibility of hidden medical illness or reduced physiological function of major organs.

From this study, it is obvious that mortality in the elderly could not have been reduced by early surgery as many died of concomitant diseases. The appearance of organ failure early in the course of conservative treatment has been regarded by some authors as an indication of the presence of necrotizing pancreatitis requiring surgical excision[15,16]. We have demonstrated previously that the appearance of organ failure did not predict the presence of necrotizing or haemorrhagic pancreatitis at operation[17]. However, the presence of hypoxia or renal failure did help to predict a fatal outcome.

In summary, the mortality of acute pancreatitis did increase with age. Some deaths were due to coincidental diseases which could not be predicted. Deaths due to biliary stones should be avoidable by diligent investigation and early elective biliary surgery. Organ failure predominated in the elderly. Thus, in the management, close surveillance of major organ function and aggressive medical treatment may be more critical in reducing the mortality rate.

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Salvage of blocked hepatic artery infusion catheters for regional therapy of metastatic liver disease

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Hepatic arterial chemotherapy for metastatic liver disease has become a practical treatment option with the advent of resealable injection ports and implantable infusion pumps. As more patients undergo this form of treatment, the ability to manage catheter-related complications such as sepsis and blockage will become increasingly important. We present two patients with catheter failure due to blockage in which we employed a novel technique to insert a replacement catheter.

Technique

Both patients underwent 'curative' resections for primary colonic carcinoma, 20 and 6 months respectively after surgery both developed hepatic metastases. In each patient a hepatic arterial infusion catheter with a resealable port (Portacath, System 320, Pharmacia, Pharmacia House, Midsummer Boulevard, Milton Keynes, UK) was implanted surgically into the gastroduodenal artery Regional fluorouracil was administered weekly and the catheter heparinized after every treatment until catheter occlusion occurred after 12 and 10 months respectively.

In both patients, catheter occlusion was shown radiographically by injecting contrast medium via the port. Aortography confirmed the site of occlusion to be at the origin of the gastroduodenal artery immediately distal to the catheter tip It also confirmed patency of the hepatic artery and demonstrated a lack of alternative branches of the hepatic artery suitable for catheter implantation At laparotomy the site of occlusion at the origin of the gastroduodenal artery was confirmed in both patients. A 5 cm segment of long saphenous vein was prepared and anastomosed end-to-side to the hepatic artery approximately 2 cm proximal to the origin of the gastroduodenal artery. The free end of the vein graft was cannulated with a replacement catheter which was positioned so that the tip lay flush with the anastomosis; the catheter was then connected to the old port (*Figure 1*)

Radiographic confirmation of catheter patency was obtained in the postoperative period by injecting contrast medium via the port.

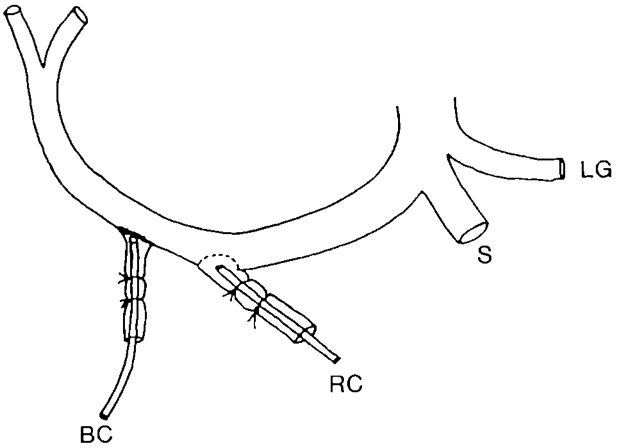

Figure 1 *Positioning and angulation of the anastomosis between saphenous vein graft and hepatic artery to allow ideal catheter placement. S, splenic artery, LG, left gastric artery, RC, replacement catheter, BC, blocked catheter*

Discussion

Catheter failure during regional chemotherapy in patients with neoplastic liver disease is extremely difficult to salvage and may be seen increasingly as more effective treatment regimens evolve. In our patients, it was not feasible to re-use the gastroduodenal artery and pre-operative angiography demonstrated the absence of alternative branches of the hepatic artery suitable for cannulation.

The direct insertion of tapered catheters via an incision in the wall of the hepatic artery secured by a purse-string suture has been described but the presence of a catheter within the lumen may predispose to hepatic arterial thrombosis. Retrograde cannulation of the splenic artery has also been described, but extrahepatic perfusion of the upper gastrointestinal tract with chemotherapeutic agents may be high when the left gastric artery is not ligated and lead to peptic ulceration or gastritis.

Use of a saphenous vein graft in the salvage of hepatic arterial perfusion catheters has not been previously described. It allows optimization of the distance between the catheter tip and the hepatic artery bifurcation (> 2 cm) so that equal perfusion of both lobes of liver can be achieved without compromising the arterial supply to the liver. Furthermore, the risk of extrahepatic perfusion can be minimized by careful placement of the anastomosis with regard to individual vascular anatomy. The use of a prosthetic conduit for a replacement catheter is a further option, but the size and compliance of saphenous vein better matches that of the hepatic artery, making it a superior choice and less likely to induce thrombosis. The saphenous vein conduit may also be a useful tool at the time of initial placement of the hepatic arterial infusion catheter when vascular anomalies make ideal catheter positioning difficult to achieve.

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Surgical management of chronic pancreatitis: long-term results in 141 patients

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The management of pancreatic pain is a controversial subject and the treatment recommended varies from one extreme to the other. Some authorities advise simply waiting for chronic pancreatitis to 'burn out', while others practise removal of the entire gland. In this paper we present 141 patients who underwent surgery for chronic pancreatitis at the Mayo Clinic. The main indication for operation was pancreatic pain and the choice of operation was based on anatomical abnormalities in the gland. The long-term results of the policy are reviewed (mean follow-up 8·5 years). Length of history, aetiology of disease, pancreatic dysfunction and pathology, time after operation and continued alcohol abuse were computer analysed for a statistically significant influence on pain relief, ability to work, pancreatic function and survival. There was one operative death (mortality rate 0·7 per cent). Continued drinking was not shown to affect postoperative pain relief but 10-year survival was significantly less in alcoholics than in those with non-alcoholic pancreatitis ($P<0{\cdot}02$*). Dilated ducts and duct calculi were associated with good results for pain relief although this association did not achieve statistical significance. Parenchymal calcification and time after operation did not influence the results of surgery. When the operation failed to relieve pain, spontaneous remission occurred in a few cases only. Seventy-seven per cent of patients had lasting relief of pain and operations selected on the basis of gross pathology were equally effective in relieving pain. Longitudinal pancreaticojejunostomy in those with dilated ducts and a Whipple operation for disease of the pancreatic head gave good results. However quality of life and pancreatic function were severely impaired by 80–95 per cent distal resections and by total pancreatectomy. An extended proximal resection is suggested for patients with diffuse disease and non-dilated ducts.*

Keywords: Surgery, chronic pancreatitis, pain relief

There is no doubt that surgery is indicated for complications of chronic pancreatitis such as biliary strictures, pseudocysts, pancreatic fistulae, duodenal stenosis and colonic obstruction. Nevertheless, the role of surgery in the treatment of intractable pancreatic pain is controversial.

Some authors[1,2] believe that lasting relief from the pain of chronic pancreatitis is a function of time and occurs 4–5 years after the onset of symptoms, when the pancreas becomes increasingly calcified and non-functional; others[3–5] report that pancreatic surgery gives immediate relief from pain in most cases, 50 per cent of whom will then be permanently pain-free. Surgery is indicated in patients with intractable pancreatic pain for two reasons: (1) the time that spontaneous remission may occur is unpredictable[2] and (2) patients who need narcotics for pain relief may become drug addicts[6].

Therefore the problem for most surgeons is not whether to operate for intractable pancreatic pain but which operation to do. Both 'poor' and 'good' results have been reported for all types of pancreatic surgery. It is not always clear if the choice of operation should depend on the cause of the pancreatitis, the nature and extent of pancreatic pathology, the risks of specific procedures or their effect on pancreatic function.

In this paper we present 141 consecutive patients with chronic pancreatitis who had an operation (performed by M.A.A and D.C.M) at the Mayo Clinic between 1958 and 1979. The main indication was intractable pain and the choice of operation was based on anatomical abnormalities in the gland. The long-term results of this policy are reviewed. Length of history, aetiology of disease, pancreatic deficiencies and pathology, time after operation and continued alcohol abuse have been computer analysed for a statistically significant influence on pain relief, pancreatic function, ability to work and survival.

Patients and methods

One hundred and forty-one consecutive patients with chronic pancreatitis undergoing surgery at the Mayo Clinic, Rochester, Minnesota, USA from 1958 to 1979, were studied. All cases of pancreatitis associated with gallstones and patients with acute pancreatitis and/or pancreatic pseudocysts as the main presenting feature were excluded. There were 79 men and 62 women, aged 15–80 years. The chief complaint in 95 per cent of patients was abdominal pain: 75 per cent had had symptoms for more than 5 years and 73 per cent required regular narcotics for pain relief before surgery. Most patients in this series had alcoholic (58 per cent) or idiopathic (30 per cent) pancreatitis. Fifteen patients had unusual causes of chronic pancreatitis. Forty-two patients had pancreatic endocrine insufficiency, twelve of whom were receiving insulin before surgery, and twenty-eight patients had steatorrhoea. Forty-one per cent of cases had pancreatic calcification on abdominal radiographs

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Table 1 *Grading of results after pancreatic surgery*

Grade of result	Pain	Activity
Excellent	Nil	Normal
Good	'Better'*	Normal
Fair	Nil, 'better'	Impaired
Poor	'Same', 'worse'	Impaired

* Less frequent, narcotics not required

Table 2 *Pancreatic pathology in 141 patients with chronic pancreatitis*

Pancreatic pathology	Patients*
Parenchyma	
Hypertrophy	77
Atrophy	9
Fibrosis	90
Calcification	35
Ducts	
Diffuse dilatation	22
Dilatation with strictures	21
Calculi	22
Sites	
Whole pancreas	63
Head	12
Body	15

* Number of patients expressed as percentage of group

The diagnosis of chronic pancreatitis was based on laboratory tests, radiographs, ultrasound, computerized axial tomography, pre-operative and intra-operative pancreatography, gross inspection of the pancreas at laparotomy and histological examination after biopsy or resection.

The final selection of operation was made at laparotomy when the extent of parenchymal and ductal changes was reassessed by exploration and/or intra-operative pancreatography. Gross anatomical abnormalities in the pancreas were recorded.

Operations for pancreatic pain

Sphincteroplasty. Thirteen patients with minimal ductal and parenchymal changes underwent sphincteroplasty as the definitive procedure. A 'double' sphincteroplasty[7] was performed for two unusual cases of benign ampullary stenosis

Duct drainage Twenty-three patients in whom the main pancreatic duct was diffusely dilated to a diameter of 7 mm or more had a drainage procedure, either longitudinal pancreaticojejunostomy[8,9] (18 cases) or a caudal pancreaticojejunostomy[10] (5 cases).

Whipple[11] operation. Ten patients in whom the pancreatic head was the dominant site of disease had a pancreaticoduodenectomy

Limited distal resection. Thirty-one patients underwent a limited 50–79 per cent distal resection These included 11 patients with dominant disease of the body and tail and 20 patients with diffuse disease and multiple strictures ('chain of lakes' variety). In the latter, resection was combined with de-roofing the ducts of the head and uncinate process and draining these into a Roux loop of jejunum.

Extended distal resection. An extended 80–95 per cent distal resection was performed in 27 patients with severe diffuse parenchymal disease· 17 had small normal ducts and 10 had proximal strictures which required caudal pancreaticojejunostomy.

Total pancreatectomy. Eight patients, six of whom had had pancreatic surgery at another hospital, underwent total pancreatectomy. Another ten patients later required total pancreatectomy when limited distal resection (four cases), extended distal resection (four cases) and ductal drainage (two cases) failed to relieve pain.

'Other' operations. Twenty-seven patients had a variety of operations alone or in combination, many of which were performed for complications of chronic pancreatitis. These 'other' operations included internal drainage of pseudocysts (nine cases), biliary–enteric bypass (eight cases), evacuation of pancreatic abscesses (seven cases), excision of pancreatic fistulae (two cases), proximal ligation of pancreatic ducts (two cases), truncal vagotomy and gastrojejunostomy (one case), splanchnic blocks (three cases), excision of a colonic stricture (one case) and duodenotomy for duodenal stenosis (one case).

Assessment of results

The results of surgery were assessed before discharge, during the first year after operation and at 2-, 5- and 10-year intervals. The number of patients reviewed at each follow-up period varied but 75 per cent were followed up for more than 5 years and 25 per cent for more than 10 years after surgery. In 1984, a questionnaire was sent to 99 patients known to be alive and to their physicians for information about abdominal pain, pain medication, activity or work status, bowel habits, diabetes and alcohol intake. Where necessary, data were obtained by telephone calls, from death certificates and autopsy records. This information was pooled with data recorded prior to 1984 and the results of surgery given for 'last follow-up'*. The mean interval between operation and 'last follow-up' was 8·5 years.

Operative mortality was defined as death within 30 days of surgery or during the same admission as the operation. 'Early' death describes those who died during the first year after operation from postoperative sequelae, pancreatitis or alcoholism. 'Early' recurrence of disease includes patients who required readmission for pancreatitis or further pancreatic surgery in the first postoperative year The number and cause of late deaths was noted. Survival was examined for the total population and for each of the six operative groups†.

The influence of aetiology and of continued drinking on survival was examined At follow-up, the degree of pain was assessed by comparison with the patient's pre-operative symptoms The effect of time on pain relief after surgery was studied in 55 patients evaluated 2–5 years post-operatively and then again 5–10 years after surgery. The ability to work or, if retired, to function normally was recorded. The results of surgery were then graded according to both pain and activity (*Table 1*)

Pre-operative and postoperative diabetic status were compared for each operative group. On follow-up, diabetes was assessed as 'worse' if the patient now had insulin-dependent diabetes, if insulin requirements had increased or if insulin-dependent diabetes had become unstable. Patients developing diabetes after discharge from hospital were noted. The presence of steatorrhoea before and after surgery in each operative group, as well as the number of patients in whom steatorrhoea became evident at follow-up, were recorded.

Special analysis. Comparisons of discrete variables were made with χ^2 tests or with Fisher's exact test when necessary. Estimates of patient survival and survivorship free of subsequent surgery were made using the method of Kaplan and Meier[12]. Comparisons between survivorships were made with the log rank test[13].

Results

Operative findings

Pancreatic ductal and parenchymal abnormalities found or confirmed at operation are recorded in *Table 2.*

Operative mortality

There was one operative death (mortality rate 0·7 per cent). This patient, a 55-year old man on steroid therapy for rheumatoid arthritis, died from pneumonia, septicaemia and postoperative pancreatitis after caudal pancreaticojejunostomy and exploration of the biliary tree.

Early deaths and recurrent disease (Table 3)

Thirteen per cent of patients in the operative groups and 15 per cent of cases undergoing 'other' operations suffered an

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* Most recent follow-up on living patients or, in those who died, the last follow-up prior to death

† Includes procedures done as the first operation after admission unless otherwise indicated. Patients undergoing 'other' operations only are excluded

Table 3 *Early deaths and early recurrence of disease*

Operation (number)	Death	Recurrent pancreatitis	Repeat pancreatic surgery
Sphincteroplasty (15)	—	3	—
Duct drainage (23)	1	2	1
Whipple (10)	—	—	—
Distal resection			
50–79% (31)	—	1	3
80–95% (26*)	—	—	4
Total			
pancreatectomy (8)	—	—	—

* One patient lost to follow-up

Table 4 *Late deaths in operative* groups*

	Causes of death		
Operation (number)	Sequelae of operation, pancreatitis, alcohol	Unrelated	Unknown
Sphincteroplasty (15)	—	4	—
Duct drainage (21)†	4	2	1
Whipple (10)	1	3	1
Distal resections			
50–79% (27)†	1	2	2
80–95% (23)†	—	2	1
Total			
pancreatectomy (18)‡	6	—	2

* 'Other' operations excluded
† Excludes cases later submitted to total pancreatectomy
‡ Total pancreatectomy as primary or secondary procedure

early death or early recurrence of disease. The percentage of early deaths plus recurrent disease was least after the Whipple operation (0 per cent) and greatest after extended distal resection (16 per cent). However, no statistical correlation was found between the operation performed and the incidence of early death or recurrent disease.

Survival

There were 41 late deaths in the total patient population. These included 12 deaths from postoperative sequelae, pancreatitis or alcoholism and 14 from unrelated causes. The cause of death is not known in 15 patients, 14 of whom were alcoholics. *Table 4* records the number of late deaths for each operative group. The expected and observed survival in this series of 141 patients with chronic pancreatitis is shown in *Figure 1*. Ten years after operation, 73 per cent of patients were still alive compared with an expected rate of survival of 91 per cent. This difference is highly significant ($P<0{\cdot}000001$).

In the total patient population, survival was significantly less in those with alcoholic pancreatitis than in non-alcoholic patients (*Figure 2*) 10 years after surgery ($P<0{\cdot}02$, log rank test). The type of operation performed did not appear significantly to influence survival free of subsequent surgery (*Figure 3*). The numbers in each operative group were too small to compare survival of alcoholic and non-alcoholic patients subjected to the same procedures. Continued drinking of alcohol at 2 years after operation was not shown to influence survival thereafter.

Relief of pain

The results of the 1984 follow-up are recorded in *Table 5* and have been pooled with data recorded before 1984 in *Table 6*. The degree of pain relief did not change with time in most of the 55 patients re-evaluated 5–10 years after surgery: of the 22 cases initially pain-free after operation, one had suffered a relapse and only 3 of 23 patients with persistent postoperative pain underwent spontaneous remission. Neither the length of history nor aetiology of the disease were found to influence significantly relief of pain at the 2-, 5- and 10-year follow-up intervals. An association between pre-existing pancreatic dysfunction (diabetes and steatorrhoea) and the number of patients with significant postoperative pain relief could not be demonstrated Continued drinking of alcohol was not shown to affect the relief of pain after operation.

Calcification of the gland parenchyma had no influence on the numbers of patients with pain relief at each of the follow-up

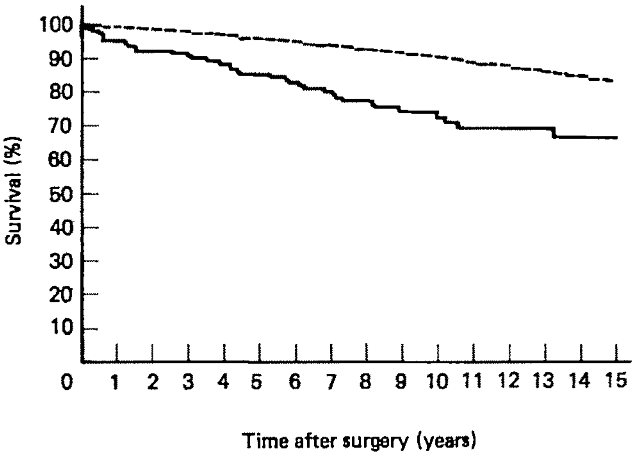

Figure 1 *Expected* versus *observed survival in patients with chronic pancreatitis.* ——, *Observed;* – – –, *expected*

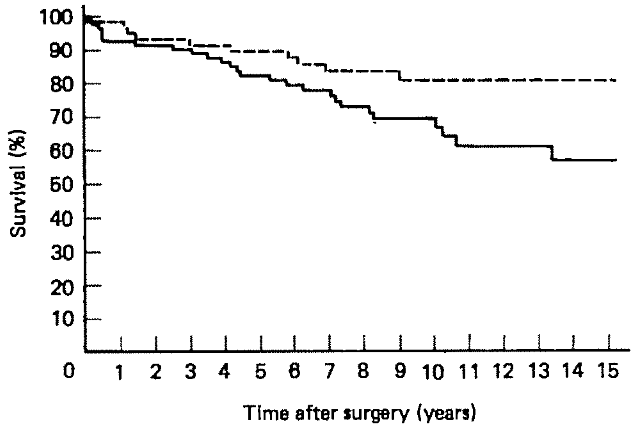

Figure 2 *Survival* versus *aetiology in patients with chronic pancreatitis.* – – –, *No alcohol,* ——, *alcohol*

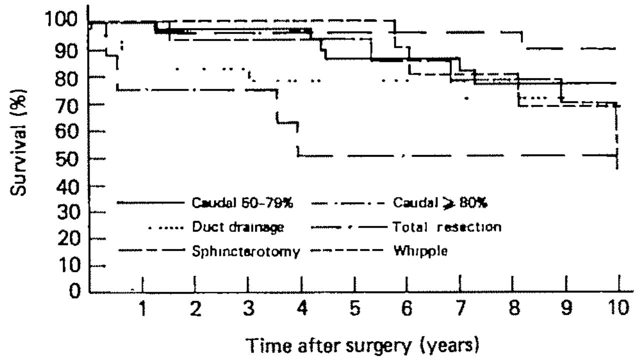

Figure 3 *Survival* versus *initial operation in patients with chronic pancreatitis*

Table 5 *Patients reviewed* in 1984*

Operation	Number of patients	Recurrent pancreatitis	Pain		Still drinking	Able to work
			Nil, better	Same, worse		
Sphincteroplasty	10	5/9	6/9	3/9	2/9	9/9
Duct drainage	12	5/11	11/12	1/12	4/10	9/12
Whipple	5	2/5	5/5	—	2/5	5/5
Distal resections						
50–79%	20	6/20	17/20	3/20	5/19	14/16
80–95%	17	6/17	12/17	5/17	6/17	8/16
Total pancreatectomy	9†	—	8/9	1/9	3/9	5/9

* Denominator includes only patients from whom information was available
† Includes five patients who had total pancreatectomy as a second operation These cases are not included in the other operative groups

Table 6 *Pain relief at last follow-up*

Operation	Patients assessed	Pain	
		Relief	No relief
Sphincteroplasty	14	9 (64%)	5 (36%)
Duct drainage	15	12 (80%)	3 (20%)
Whipple	9	9 (100%)	—
Distal resections			
50–79%	23	19 (83%)	4 (17%)
80–95%	22	15 (68%)	7 (32%)
Total pancreatectomy	17*	13 (76%)	4 (24%)
Total	100	77	23

* Total pancreatectomy as primary or secondary procedure. These cases are not included in the other operative groups

Table 7 *Activity status at last follow-up*

Operation	Patients assessed	Activity	
		Normal	Impaired
Sphincteroplasty	12	10 (83%)	2 (17%)
Duct drainage	13	9 (69%)	4 (31%)
Whipple	7	7 (100%)	—
Distal resections			
50–79%	20	18 (90%)	2 (10%)
80–95%	20	9 (45%)	11 (55%)
Total pancreatectomy	14*	5 (36%)	9 (64%)

* Total pancreatectomy as primary or second procedure These cases are excluded from the other operative groups

periods. The number of patients with stones in the main pancreatic duct who had relief of pain after operation was greater than those without duct stones, but the difference was not significant.

At both the 2- and 5-year follow-up periods a slightly larger proportion of patients with dilated ducts noted at operation had pain relief compared with patients without ductal dilatation. Ten years after surgery, 93 per cent of those with dilated ducts had relief of pain compared with 75 per cent of those with normal or narrowed ducts although this difference failed to achieve statistical significance.

The ability to work or, if retired, to function normally at the time of last follow-up is presented in *Table 7*. The degree of pain relief is combined with activity status to grade the overall results of surgery at the last follow-up and reported in *Table 8*. The incidence of diabetes and steatorrhoea before and after surgery and on follow-up is detailed in *Tables 9* and *10*, respectively

Table 8 *Grade of results of last follow-up*

Operation	Patients assessed	Grade of result			
		Excellent	Good	Fair	Poor
Sphincteroplasty	8	3	3	1	1
Duct drainage	13	7	2	1	3
Whipple	7	5	2	—	—
Distal resections					
50–79%	19	14	3	—	2
80–95%	18	5	2	7	4
Total pancreatectomy	14*	2	3	6	3

* Total pancreatectomy as primary or second procedure. These cases are excluded from other operative groups

Discussion

Many patients with chronic pancreatitis can be managed conservatively with non-narcotic analgesics, withdrawal of alcohol, treatment of diabetes and enzyme replacement therapy[14]. However, when medical management fails and the patient has severe, unremitting pain, operation must be considered. For most patients in this series, surgery was the 'last resort': 75 per cent had suffered intractable pain for more than 5 years and needed regular narcotics for pain relief. An operation, therefore, can be justified on the grounds that it is unethical to withhold surgery from a patient with intractable pain[15], but the following questions need to be answered:

1 How many patients have immediate and lasting relief of pain after operation? Is there any evidence to suggest that the long-term results of surgery are unrelated to the procedure performed and are due to the disease 'burning out'? Should patients who cannot stop drinking undergo operations for pain relief?
2 Are anatomical abnormalities in the pancreas a reliable guide to choice of operation? Does the type of pancreatic pathology influence the results of surgery?
3. At what cost, in terms of morbidity, mortality and survival, is pain relief achieved by different operations?

Although this report suffers the limitations of a retrospective review it does provide data on the results of pancreatic surgery 5 to 25 years after operation, which may help to answer these questions.

Relief of pain

In this series, 60 per cent of patients had immediate *and* lasting pain relief after operation. Surgery failed to relieve pain in 23 per cent of cases and another 17 per cent had relief of pain only after recurrent attacks of pancreatitis. However, duration of disease, pancreatic calcification, pancreatic deficiencies and time after operation could not be correlated with the incidence of pain relief. When surgery failed to relieve the patient's

Table 9 *Incidence of diabetes in operative groups*

Operation (total cases)	Pre-operative diabetes	Postoperative diabetes	Last follow-up: Patients reassessed	Last follow-up: Diabetes 'worse'	Last follow-up: New cases
Sphincteroplasty (15)	0	0	13	—	3
Duct drainage (23)	3	3	13	1	1
Whipple (10)	1	2	9	1	2
Distal resections					
50–79% (31)	7	10	22	3	2
80–95% (27)	1	17	22	4	2
Total pancreatectomy (8)	3	8	15*	4	—

* Includes ten patients who had total pancreatectomy as a secondary procedure

Table 10 *Incidence of steatorrhoea in operative groups*

Operation (total cases)	Pre-operative steatorrhoea	Postoperative steatorrhoea	Last follow-up: Patients reassessed	Last follow-up: New cases of steatorrhoea
Sphincteroplasty (15)	3	3	13	1
Duct drainage (23)	7	7	13	3
Whipple (10)	2	3	9	2
Distal resections				
50–79% (31)	10	16	23	5
80–95% (27)	8	14	20	5
Total pancreatectomy (8)	8	8	11*	—

* Includes ten patients who had total pancreatectomy as a secondary procedure. All patients had steatorrhoea after total pancreatectomy

symptoms, spontaneous remission occurred in a few cases only. This suggests that the long-term results of surgery in most patients were related to the operation performed and not to the disease burning out.

The wisdom of operating for pancreatic pain in chronic alcoholics has been questioned[15], many authors[4,16–18] reporting poor results in patients who continue to drink. Others[19,20], however, have found no association between postoperative pain relief and abstinence from alcohol. The current series also failed to correlate continued drinking with persistence of pain after operation. It is possible that some patients concealed their drinking habits and that poor results of operations in chronic alcoholics may have been missed by incomplete follow-up. However, until it is clearly established that surgery in the chronic alcoholic with intractable pancreatic pain offers little or no prospect of postoperative pain relief, the indications for operation must be assessed on an individual basis.

Choice of operation

The mechanism of pancreatic pain is poorly understood, pain being associated with a wide spectrum of pathological changes in the pancreas (*Table 2*). It is even less clear why drainage of pancreatic ducts and/or resection of diseased parenchyma relieves pain[15], yet most surgeons base selection of operations for pancreatic pain on the anatomical changes in the pancreas. The results of our review support this policy of selection: we found no significant difference in the incidence of pain relief between the six operative groups. Operations selected on the basis of gross pancreatic pathology appear to be equally effective in relieving pain, a finding which has been previously reported[4]. But the type of pancreatic pathology itself may influence the results of surgery: in common with other series[3,5], dilated ducts and duct calculi were associated with a larger number of good results, although the association did not achieve statistical significance in this study.

Morbidity and mortality

The numbers in each operative group were small and operative mortality, incidence of early death or early recurrence of disease could not be correlated with the procedure performed. The most striking difference between the operations was their effect on pancreatic function and the quality of life. As expected, sphincteroplasty and ductal drainage had no effect on endocrine or exocrine status in the postoperative period. Ten per cent of patients suffered deterioration in pancreatic function after Whipple operations. This, however, compares favourably with the immediate results of distal and total pancreatectomies. Diabetic status was 'worse' in 23 per cent of limited distal resections, in 59 per cent of extended distal resections and in 63 per cent of total pancreatectomies. The postoperative incidence of steatorrhoea was also greater in patients who had distal resections than in those undergoing a Whipple operation. Two facts may account for these differences: the Whipple operation removed less than half of the gland and preserved the distal pancreas with its greater concentration of islet cells. For the same reasons, deterioration in pancreatic function on follow-up was more frequent after distal resections. Long-term changes in exocrine and endocrine status were least after sphincteroplasty, performed for minimal disease, and occurred in 21 per cent of the ductal drainage group, reflecting the progressive nature of chronic pancreatitis.

In this review, quality of life after surgery can be inferred from the results when these are graded both by degree of pain relief and by activity status. Impairment of activity was most common after extended distal resection and total pancreatectomy. Reasons for this include disabling steatorrhoea and difficulties with insulin therapy. This impairment of activity is the explanation for large numbers of patients graded as 'fair' only after these two operations. Although the incidence of significant pain relief was similar in all operative groups, quality of life was obviously worse after total pancreatectomy and extended distal resection.

Survival

Chronic alcoholic pancreatitis has an appreciable late mortality, irrespective of treatment[21], and the influence of alcoholism was clearly evident 10 years after surgery: survival of alcoholic patients was significantly less than that of patients with non-alcoholic pancreatitis. However, in contrast to other reports[4,5,22,23] continued drinking after operation was not found to influence survival, but follow-up of alcoholic patients is notoriously unreliable[6] and we may have failed to identify all of those still drinking.

When a patient with chronic pancreatitis undergoes surgery, it is essential to know whether the operation performed increases the late mortality rate. In this series, the operation selected had no significant influence on survival free of subsequent surgery. It was only when the results of both primary and secondary procedures were examined that there appeared to be a difference between the operations. Late deaths related to postoperative sequelae, pancreatitis or alcohol were most frequent in patients who had a total pancreatectomy. Three of these late deaths occurred in alcoholics unable to manage their diabetes. Another patient is known to be institutionalized with brain damage due to hypoglycaemic attacks after total pancreatectomy. This operation should be considered only in rehabilitated patients when other procedures have failed to relieve severe and disabling pain.

This paper presents the long-term results of operations for pancreatic pain. Most of the operations are in current use although others, like sphincteroplasty and the Du Val procedures, have fallen into disfavour[15]. Longitudinal pancreatojejunostomy will drain the pancreatic ducts more effectively than the (Du Val) caudal pancreaticojejunostomy but our results suggest that there may still be a place for sphincteroplasty in patients with minimal ductal and parenchymal changes.

The review has confirmed observations made in earlier studies and supports the thesis that surgery has a role in the management of intractable pancreatic pain where there is no evidence of chronic pancreatitis burning out. Good results can be expected for ductal drainage in those with dilated ducts and duct calculi. Major pancreatic resections also give relief from pain but the quality of life after operation can be seriously impaired by the type of resection performed.

Total pancreatectomy is rarely indicated in patients who are still addicted to alcohol or drugs and incapable of managing their insulin therapy. Patients undergoing an extended distal resection can be chronically disabled by this operation. By contrast, there were no early deaths or early recurrence of disease after the Whipple operation in this series: almost all patients had significant pain relief and were able to return to work. Pancreaticoduodenectomy is the procedure of choice where the major locus of disease is the pancreatic head. Preservation of the tail of the pancreas will limit the number of patients with postoperative diabetes and may help to reduce the rate of deterioration in endocrine functions. Therefore, an extended *proximal* resection should be considered for patients with diffuse disease and non-dilated ducts. Provided that both the Whipple operation and distal resection can be performed with comparably low operative mortalities, a prospective randomized trial to compare these two procedures may be indicated for this group of patients.

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Subcostal incision versus midline laparotomy in gallstone surgery: a prospective and randomized trial

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We report the results of a prospective and randomized trial designed to study the incidence of abdominal and pulmonary complications in gallstone surgery comparing subcostal (SI) with midline incision. The need for postoperative analgesia was lower in the SI group. There was no difference in the degree of hypoxaemia in the first two postoperative days, but there was less impairment of pulmonary function in terms of vital capacity and forced expiratory volume in 1 s ($P < 0{\cdot}0001$) *in the SI group. SI patients also had a lower incidence of pulmonary or abdominal complications but the difference was not significant. Finally, we found a reduced hospital stay for the SI patients* ($P < 0{\cdot}01$)*, probably related to a reduced postoperative analgesic requirement and an improved pulmonary function. We conclude that subcostal incision is a better approach for biliary tract surgery and should be used whenever possible.*

Keywords: Abdominal incisions, postoperative pulmonary function, gallstone surgery, morbidity

Choice of surgical incision in the abdomen is determined by the adequacy of the access afforded.

Upper abdominal transverse incisions are thought to be followed by fewer complications than midline incisions[1–5], but reports are controversial. While some authors have found that transverse incisions had a lower complication rate in terms of local complications (wound infection, wound dehiscence and incisional hernia) and pulmonary complications (atelectasis, lung infection, hypoxaemia)[3,5,6], others believe that there are other factors that are more important than the type of the incision (pre-operative pulmonary dysfunction, postoperative ventilatory depression, hypovolaemia and inhalation of gastric contents)[4]. The majority of these studies include a variety of diseases, which makes the results difficult to interpret.

In order to elucidate the influence of the type of incision in the incidence of abdominal and pulmonary complications, we designed a prospective and randomized trial, to study the postoperative pain, pulmonary function, morbidity and hospital stay in gallstone surgery.

Patients and methods

A total of 132 patients were randomized, and of these 129 were operated on for cholelithiasis and/or choledocholithiasis. Elective and emergency patients were separately randomized in order to assure a similar number of emergency cases in both groups. Three patients previously allocated to the subcostal incision (SI) group were excluded: two because operation was not performed, and another because of the coexistence of an epigastric hernia. A subcostal incision 15 cm long was made in 63 patients and a midline laparotomy (ML) approximately 20 cm long was made in 66 Methods of closure were standardized for both incisions. SIs were closed in two layers, a continuous Dexon® (Braun–Dexon, Barcelona, Spain) Nr.0 suture for peritoneum and posterior fascia, and interrupted Dexon Nr 0 sutures for muscle and anterior fascia MLs were closed with one-layer interrupted Dexon No.0 sutures *Table 1* shows the comparison of the two groups in terms of sex, age, weight, elective and emergency surgery. *Table 2* shows the incidence of the associated risk factors of diabetes, hypertension, cardiomyopathy, liver disease, renal failure and chronic obstructive airways disease (COAD); almost one-third of the patients in each group had at least one risk factor.

All operations were performed under general anaesthesia (thiopentone induction, endotracheal intubation, relaxants and halothane/oxygen/nitrous oxide inhalation with mechanical ventilation). Postoperatively, pain was controlled by analgesic injections (meperidine, 1 mg/kg of body weight) on demand, and the number of doses was recorded. Three different ward nurses were in charge of analgesic injections (one in each period of duty); they were aware that a study was in progress but did not know the purpose of the protocol

Pulmonary function studies included vital capacity (*VC*) and forced expiratory volume in 1 s (FEV_1) using a spirometer (VITALOGRAF® (Vitalograph Ltd, Beckingham, UK)) and were performed in the sitting position. Determinations were made the day before operation, immediately in the recovery room, at 24 h and on the seventh day In order to avoid the effect of postoperative pain, the patients received an analgesic injection (meperidine 1 mg/kg IM) 30 min before each study In 20 patients in each group arterial oxygen and carbon dioxide partial pressures (P_{a,O_2} and P_{a,CO_2}) were determined (pre-operatively, and on days 1, 2 and 5). The alveolar–arterial O_2 pressure difference P_{Aa,O_2}) was calculated using the formula

$$P_{Aa,O_2} = ((BP - 47)FI_{O_2} - P_{a,CO_2}/0\,8) - P_{a,O_2}$$

where *BP* was atmospheric pressure on the day of sampling (the value 47 corresponds to the H_2O vapour pressure) and FI_{O_2} was the fractional inspired oxygen concentration[7]. (Normal range for the P_{Aa,O_2} value is between 10 and 20)

Table 1 *Comparability of the groups*

	Midline ($n = 66$)	Subcostal ($n = 63$)	
Sex M/F*	30/36	27/36	n s
Age†	59·2 ± 15	61·2 ± 15	n s.
Weight†	64·3 ± 3	64·2 ± 4	n s
Elective/emergency*	56/10	51/12	n s.

Values are expressed as the mean ± s.e.m.: *χ^2 test, †*t* test

Table 2 *Associated risk factors*

	Midline laparotomy	Subcostal incision	n s
Diabetes*	5	6	n s
Hypertension*	3	7	n.s.
Cardiomyopathy*	6	3	n.s
Renal failure†	2	1	n.s.
Liver disease†	2	4	n s
COAD*	4	5	n.s
Patients involved	14/66	20/63	n.s

* χ^2 test; † Fisher's exact test, COAD, chronic obstructive airways disease

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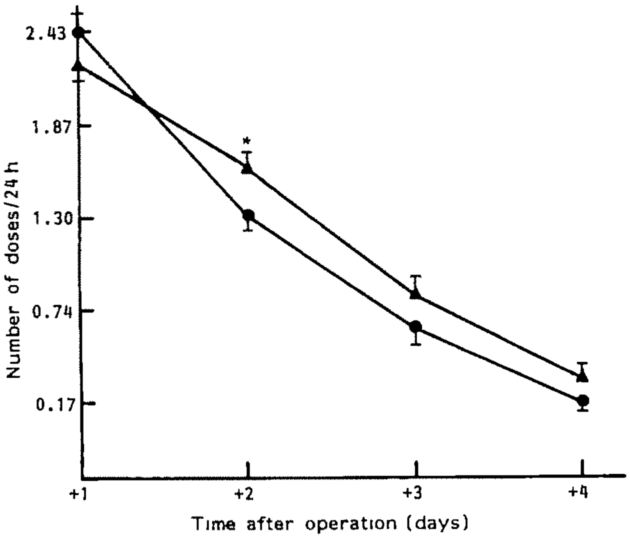

Figure 1 *Postoperative analgesia. Values are mean number of doses per 24 h ± s.e.m The need was lower in the subcostal incision group, reaching statistical significance only on the second postoperative day.* *P=*0·0013.* ●, *Subcostal incision group,* ▲, *midline incision group*

We evaluated the presence of any type of pulmonary or abdominal complication. Pulmonary complications were only considered when there were symptoms and/or radiological evidence (pleural effusion, pneumonia or atelectasis) which needed medical treatment. Infection was recorded when there was purulent discharge from the wound. (Antibiotic prophylaxis was established with cefoxitin 6 g (2 g at the induction of anaesthesia, 2 g at 2 h after the induction and 2 g at 4 h after the induction).)

Statistical analysis was done using the SPSS statistical package and an IBM 3083-XE computer. Student's t test, Mann–Whitney U test or the χ^2 test were used when appropriate, a P value of 0 05 being accepted as significant. Pulmonary function studies were analysed by profile analysis (Analysis of Variance) using the Hotellings' statistic.

Patients were followed up to 4 months from the day of operation.

Results

One patient in the SI group was excluded from analysis because of the presence at laparotomy of a biliary tract cancer, and one was excluded in the ML group because of the coexistence of a duodenal ulcer.

Pre-operative pulmonary function in terms of VC and FEV_1 was similar in both groups. The mean (± s.e.m.) value (in ml) for VC in ML patients was 2631 ± 158, while in the SI patients it was 2543 ± 138. On the other hand, the FEV_1 value (in ml) for the ML group was 2202 ± 147 and for the SI group was 2083 ± 121. These figures are within the normal range when corrected for sex, age and height, for each patient[8]. Finally, $P_{\mathrm{Aa,O_2}}$ values (in mmHg) were not significantly different between groups (t test); for ML patients the mean (±s.e.m.) was 18·5 ± 3·6 and for SI patients it was 16·1 ± 2·3.

There were 15 patients with choledocholithiasis in each group. There was no difference in surgical technique ($\chi^2 = 1{\cdot}461$, d.f. = 2 and $P = 0{\cdot}481$) between the two groups, with respect to cholecystectomies alone (48 in ML *versus* 46 in SI), common bile duct explorations (17 in ML *versus* 16 in SI), T tube drainage (11 in ML *versus* 7 in SI) or choledochoduodenostomies (6 in ML *versus* 9 in SI).

Postoperative analgesia

Figure 1 shows the need of analgesia in number of doses/24 h. The need in the SI group was always lower (except for the first day) than that in the ML group; but the difference is only significant on day 2 (U value = 1446·5 and $P = 0{\cdot}0013$).

Postoperative pulmonary function

For both types of incision a significant decrease in FEV_1 and VC was observed. *Figures 2* and *3* show progression of both FEV_1 and VC in SI and ML groups. The decrease was always greater in the ML group: immediate, day 1 and day 7 figures were statistically significant. Profile analysis showed no difference in the trend over the days studied (parallelism hypothesis). On the other hand, mean values were statistically different for FEV_1 ($F = 15{\cdot}15$) and VC ($F = 13{\cdot}18$). Both studies showed a P value $<0{\cdot}0001$

The $P_{\mathrm{Aa,O_2}}$ difference increased in both groups (*Figure 4*). The increase was similar on days 1 and 2, but on day 5 the $P_{\mathrm{Aa,O_2}}$ difference was more marked in the ML group. Nevertheless, profile analysis failed to show any significant difference, either in the trend (parallelism hypothesis) or in the mean values obtained ($F = 0{\cdot}07$, $P = 0{\cdot}797$).

Postoperative complications

In *Table 3* the morbidity of the series is displayed. There were no deaths. Complications were experienced by two patients in the

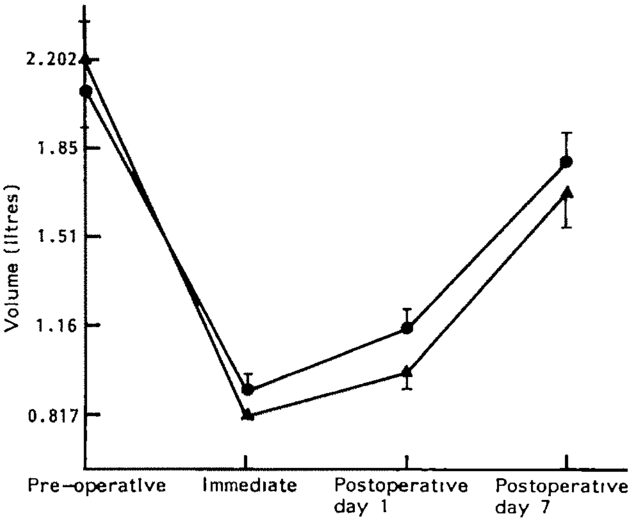

Figure 2 *Progression of forced expiratory volume in 1 s (litres) in both groups. Each point corresponds to the mean of the absolute values ± s.e.m. Profile analysis showed a significant difference between mean values with* F=*15 15 and* P<*0 0001* ●, *Subcostal incision group,* ▲, *midline incision group*

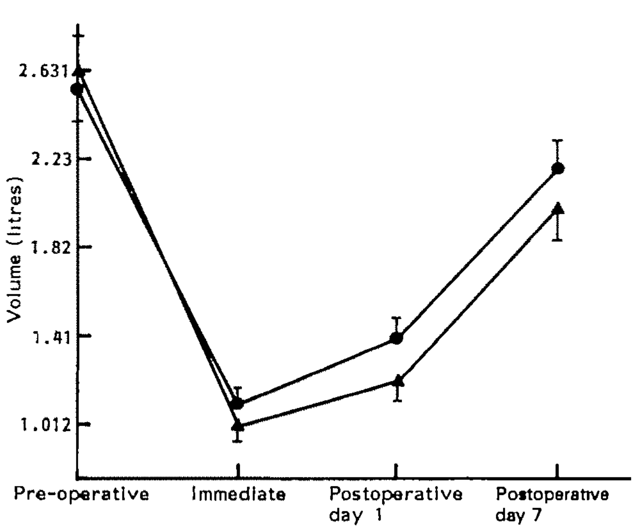

Figure 3 *Progression of vital capacity (litres) in both groups. Each point corresponds to the mean of the absolute values ± s e m. Profile analysis showed a significant difference between mean values with* F=*13 18 and* P<*0·0001.* ●, *Subcostal incision group,* ▲, *midline incision group*

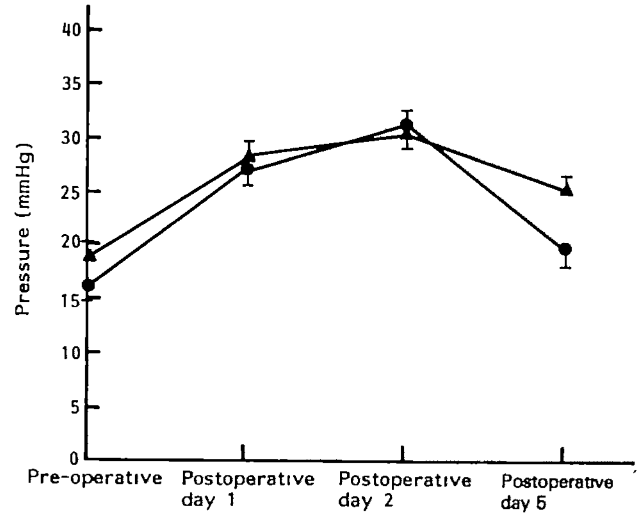

Figure 4 *Alveolar-arterial oxygen pressure difference in mmHg ±s e m. Progression is similar in both groups on days 1 and 2. On day 5 subcostal incision group reaches normal values. Profile analysis failed to demonstrate any difference between groups* (F=0·07, P=0·797). ●, *Subcostal incision group;* ▲, *midline incision group*

Table 3 *Morbidity*

	Midline laparotomy	Subcostal incision	*P*
Pulmonary	5	1	n.s.
Wound infection	2	0	n.s.
Intra-abdominal abscess	0	1	n.s.
Wound disruption	1	0	n.s.
Incisional hernia	2	0	n.s.
Patients with complications	10/65	2/62	<0·05

SI group and 10 in the ML group ($P<0·05$). Pulmonary complications, although more frequent in the ML group (5 *versus* 1), did not reach statistical significance and the same was the case with abdominal complications: i.e. with wound infection, intra-abdominal abscess, wound disruption, and incisional hernia there were no statistically significant differences between groups, individually or collectively.

Hospital stay

Hospital stay was much longer in patients with a midline laparotomy. In the ML group it was 10·1±1·1 days and in the SI group it was 8·5±1·2 days, and this difference is statistically significant ($t=2·841$, d.f.=126 and $P<0·01$).

Discussion

Although it is well known that upper abdominal wall incisions lead to a short-term reduction of the pulmonary function with alterations in gas exchange, the influence of the type of incision remains controversial[3–7]. Our study shows that the need for postoperative analgesia and the degree of respiratory impairment seems to be less in patients with a SI. Pulmonary complications are probably less frequent because a lower intensity of postoperative pain permits abdominal muscle function with respiration. Becquemin *et al.*[6] were not able to demonstrate any effect, except for those with chronic obstructive pulmonary disease. In our study pulmonary function is consistently worse in patients with a ML. In contrast with Becquemin *et al.*[6] and Ali and Ali Khan[10], we have demonstrated a better postoperative pulmonary function (in terms of *VC* and FEV_1) in patients with a SI, although their pre-operative values were within normal ranges (when corrected for sex, age and height)[8]. We have not been able to find any difference in the $P_{\mathrm{Aa},\mathrm{O}_2}$, at least in the first two postoperative days. On the other hand, on day 5 the $P_{\mathrm{Aa},\mathrm{O}_2}$ in the SI group was almost normal, in contrast with the ML group which remained high. Although this indicates a ventilation–perfusion mismatch (generally attributed to several factors, including prolonged supine position, immobilization and low ventilation perfusion ratio secondary to airway narrowing or closure in dependent lung zones[10–12]), it does not explain how hypoxaemia could play a part in the incidence of pulmonary complications, as suggested by Becquemin *et al.*[6], since it was similar in the first 2 days.

The incidence of complications was much higher in the ML group. We have not been able to show a statistical difference in the incidence of pulmonary or abdominal complications; this probably relates to the number of patients studied. The wound complications may have influenced postoperative pulmonary function.

It is interesting to observe that there was no wound dehiscence or incisional hernia in the SI group. These results are very similar to those of Greenall *et al.*[1,4] who found that out of 579 major laparotomies there were two burst abdomens and nine incisional hernias in the ML group, whereas in the transverse incision group there were only two incisional hernias This fact has been very well studied by Letwin *et al*[13]; these authors found that the distracting force on a vertical incision during activity in the postoperative period is nearly twice as great as that on a transverse incision.

Hospital stay was significantly longer in patients with a ML which suggests that total costs were lower in patients with a SI.

We conclude that SI is a better approach for biliary tract surgery and is associated with better postoperative pulmonary function and a lower incidence of complications.

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Short note

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476

Effect of drainage on subhepatic collections and respiratory function after elective cholecystectomy

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Although cholecystectomy without drainage is not new, over 90 per cent of surgeons still consider a drain necessary[1] to prevent subhepatic fluid collections and basal atelectasis[2]. Two recent studies have prospectively examined the incidence of ultrasound detected subhepatic collections after cholecystectomy: one showed a higher and the other a lower incidence when a drain was omitted[3,4]. The effect of drainage on the incidence of basal atelectasis is uncertain. This study prospectively examines the effect of drainage of the gallbladder bed on the incidence of subhepatic fluid collections and basal atelectasis.

Patients

One hundred consecutive patients undergoing elective cholecystectomy without exploration of the common bile duct were studied The trial was approved by the local ethical committee and all patients gave informed consent.

A single dose (1·5 g) of intravenous cefuroxime was given at induction of anaesthesia. A subcostal or transverse incision was made and cholecystectomy performed using a standardized technique. Operative cholangiography was performed via the cystic duct Needle puncture of the common bile duct was avoided. The cystic duct and artery were ligated with polyglactin. Haemostasis was achieved and only at this stage was randomization made If a drain was stipulated, a latex tube drain (8 mm external diameter) was brought out through a stab wound more than 2·5 cm from the main wound. The tip was placed near the gallbladder fossa in Morison's pouch. It was immediately connected to a sealed bag. All drains were removed within 3 days

Liver function tests and peak expiratory flow rate were measured on the day before and on the first and fourth days after operation Between the third and fifth days, a chest X-ray was taken and an ultrasound examination of the subhepatic region performed The drain site (or an equivalent position of normal skin) was covered with an adhesive plaster, so that the radiologist was unaware whether or not a drain had been used. All wounds were examined at discharge from hospital and at review 1 month later.

Results

There were nine subhepatic fluid collections (three undrained and six drained; Fisher's exact test, $P = 0{\cdot}49$). One patient in each group had a fluid collection > 5 cm in maximum diameter. None of the collections was clinically obvious or significant. There were three wound infections (two in the drained group). After operation minor changes in liver function tests were common, but were not related to the presence or absence of a drain. Eleven patients had clinical and/or radiological evidence of basal atelectasis; eight of these patients had a drain (χ^2 on 1 d.f. with Yates' correction $= 1{\cdot}41$, $P = 0{\cdot}23$).

The peak flow rate (l/min) was similar in the two groups (drain *versus* no drain) before ($4{\cdot}13 \pm 1{\cdot}0$ *versus* $4{\cdot}15 \pm 1{\cdot}1$), and on the first ($2{\cdot}01 \pm 0{\cdot}9$ *versus* $2{\cdot}22 \pm 1{\cdot}1$) and fourth days after operation ($3{\cdot}53 \pm 1{\cdot}0$ *versus* $3{\cdot}71 \pm 1{\cdot}1$).

Discussion

The continued use of drains, in the face of clear evidence that they do no good, is presumably a counsel of caution and not perfection: 'It is better to have it and not need it, than to need it and not have it.' However, very large series of cholecystectomies have been performed safely without drainage[5,6]. Maull *et al.* detected collections in 5 per cent of drained patients and 20 per cent of undrained patients though none of these collections was symptomatic[3]. Monson *et al.*, in a comparable study, found collections in 18 per cent of drained and 1·8 per cent of undrained cases, a result similar to our own[4].

Small subhepatic fluid collections are common after cholecystectomy. The use of a drain does not protect against them. We have therefore abandoned routine drainage after elective cholecystectomy.

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Food intake and nutritional status after total gastrectomy: results of a nutritional follow-up

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We studied dietary intake and nutritional status of 23 patients for 6 months after total gastrectomy with Roux-en-Y reconstruction. At discharge, patients were instructed to keep to recommended dietary allowances (RDA) and to record food intake on a specific form twice weekly. Nutritional follow-up was performed monthly and consisted of a computerized determination of food intake and of a nutritional assessment. The average daily energy intake was 6·10 MJ (1457·9 kcal) in the first postoperative month and 8·87 MJ (2118·4 kcal) in the sixth (P < 0·0005). In the first monthly follow-up no patient reached RDA. By the sixth month mean daily calorie intake was ≥ RDA in 14 patients (group A), while 9 patients (group B) did not reach RDA. A significant increase in body weight, serum albumin, total iron binding capacity and arm muscular circumference was observed in group A, while a significant decrease in body weight and arm muscular circumference was noted in group B. Moreover, of the seven patients who showed weight loss at 6 months only one was from group A. These data indicate that malnutrition is not an inevitable consequence of total gastrectomy and can be prevented by an adequate calorie intake. A close relationship between dietary intake and postoperative nutritional parameters was observed. In gastrectomized patients a strict nutritional follow-up is very important to obtain an adequate dietary intake.

Keywords: Total gastrectomy, food intake, nutritional status

Malnutrition, considered as weight loss, is the most frequent complication of total gastrectomy (TG)[1–4]. In the past, malnutrition after TG was attributed to malabsorption due to bacterial overgrowth, mucosal lesions of the small intestine, relative pancreatic enzyme insufficiency and shortened small intestinal transit time[5–10]. In 1975, Bradley[11] suggested that malnutrition after TG is due to an inadequate calorie intake, rather than to maldigestion or malabsorption. Pellegrini[12] demonstrated that patients who underwent TG can eat meals of normal size and that the transit of food through the small intestine is slower than in control subjects.

Our group has previously reported that malnutrition after TG is not common if an adequate calorie intake is maintained and that malabsorption is not a major clinical problem in gastrectomized patients[13].

In this paper we report the results in a 6-month postoperative period of a nutritional follow-up with a computerized analysis of the food intake, performed in 23 gastrectomized patients. The aim of this work is to verify the ability of gastrectomized patients to take sufficient quantities of nutrients and to quantify the relationship between dietary calorie intake and nutritional status after TG.

Materials and methods

Between September 1984 and March 1986, 36 patients underwent TG at our institution. The indications for TG were cancer of the stomach in 35 patients and Zollinger–Ellison syndrome in one patient. Four cancer patients had distant metastases at the time of TG and were not considered fit for the study, because persistence of the neoplastic disease can alter the nutritional status and dietary intake postoperatively. Of the remaining 32 patients, 8 were lost to the study and 1 died of myocardial infarction. The remaining 23 patients (13 men and 10 women), ranging in age from 27 to 76, were included in the study. Of the 12 neoplastic patients with metastases to the lymph nodes, 3 patients refused further treatment, 3 patients did not undergo chemotherapy because they were aged more than 70 years, 6 patients underwent chemotherapy (FAM).

The surgical reconstructive procedure used was the end-to-side Roux-en-Y oesophagojejunostomy in all patients. The average postoperative stay was 15·94 ± 5·48 days (range 11–35).

At discharge, patients were instructed to keep to a high protein, high calorie diet, with small and frequent meals. We did not give a dietary schema to the patients, who were invited to feed *ad libitum*, but a list of the most common foods with a high calorie content was supplied. For each of these foods, we reported the content of calories, proteins, fats, and carbohydrates.

The suggested daily energy intake was 10·05–11·30 MJ (2400–2700 kcal) for men and 7·12–8·37 MJ (1700–2000 kcal) for women, in accordance with recommended dietary allowances (RDA). Patients were instructed to measure and record all food intake on a special form, twice weekly, the relative quantities were expressed in grams, millilitres, and in spoons, glasses, cups, etc.

Nutritional follow-up was performed monthly. Firstly, a computerized determination from the patients' forms of the content of calories, proteins, fats and carbohydrates was taken. If necessary immediate steps to improve dietary intake were pointed out. Secondly, we assessed nutritional parameters: body weight (BW), triceps skinfold (TSF) (normal values ≥ 10·0 mm for men and ≥ 13·2 mm for women), arm muscular circumference (AMC) (normal values ≥ 20·2 cm for men and ≥ 18·6 cm for women) serum albumin (SA) (normal values ≥ 3·5 g/dl), total iron binding capacity (TIBC) (normal values ≥ 250 μg/dl).

A check of blood chemistry was performed quarterly. In the patients who underwent chemotherapy, the dietary forms referring to the seven days after treatment were not included in the study. A database containing the composition and the calorific value of hundreds of foods in current use is the source of a computerized analysis of the patients' dietary intake. The computer analyses several periods of time and offers a mean value daily intake in kilocalories and kilojoules, water, proteins, carbohydrates, fats, iron and electrolytes. In the evaluation of the results obtained by computerized analysis of the dietary forms we compared the average values of the first and sixth postoperative months.

Patients were then divided in two groups, based on mean daily calorie intake in the sixth postoperative month. Group A patients reached RDA; group B patients did not reach RDA.

The comparison of the mean dietary intakes on the first and on the sixth postoperative months was carried out by Student's *t* test. The statistical analysis of the variations of the nutritional parameters with

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time in groups A and B was carried out by the Student's *t* test for paired data.

Results

In *Table 1* the mean dietary intake and number of meals in the first and sixth postoperative months are shown. In the first postoperative month, no patient's average daily energy intake exceeded RDA, only two patients (9 per cent) exceeded 7·12 MJ/day (2000 kcal), while 14 patients (61 per cent) did not reach 6·28 MJ/day (1500 kcal). In the sixth postoperative month, 14 patients (61 per cent) exceeded RDA and only one patient (4 per cent) did not reach 6·28 MJ/day (1500 kcal). By comparing first and sixth postoperative months the average increase of dietary energy intake was 2·76 MJ/day (660·48 kcal) (+45·3 per cent, $P<0\cdot0005$), and only one patient did not improve his performance. No difference was observed in the number of meals taken.

Table 1 *Number of meals and calorie intake (mean ± s.d.) referred to first and sixth postoperative month*

Patient no.	No. of meals/day		Postoperative dietary intake (kcal/day)	
	first month	sixth month	first month	sixth month
1	6	6	2067±281	3107±348
2	6	6	1496±302	2810±397
3	5	5	1265±243	2004±383
4	5	5	1974±335	2599±410
5	6	5	1358±274	2017±348
6	4	5	1967±221	2016±288
7	5	6	1192±197	2592±373
8	6	6	1686±315	2514±349
9	5	5	2141±281	2751±415
10	6	6	1605±300	2405±420
11	6	6	1100±253	2696±317
12	5	5	1650±299	2092±285
13	6	6	1150±271	2095±315
14	4	4	1631±244	2300±347
15	5	5	825±170	1850±284
16	4	5	1303±204	1507±242
17	4	5	826±139	1750±302
18	4	5	1071±222	1276±248
19	4	5	1368±281	1607±279
20	4	5	1448±269	1708±244
21	6	5	1058±213	1519±251
22	5	5	1404±277	1800±284
23	4	4	1951±338	1711±249
Mean	5·0	5·2	1458·08	2118·56
s.d.	0·8	0·5	383	490
*P**	n.s		<0·0005	

* Student's *t* test for paired data

With regard to the main dietary constituents, the average daily intake was 65·30 g in the first and 87·56 g in the sixth postoperative month for proteins (+34·1 per cent, $P<0\cdot005$), 51·91 g and 69·60 g for fats (+34·1 per cent, $P<0\cdot025$), 175·60 g and 266·17 g, for carbohydrates (+51·6 per cent, $P<0\cdot0005$).

The average dietary intake by the sixth postoperative month was ⩾RDA in 14 patients (group A), while 9 patients did not reach RDA (group B).

The postoperative modifications of BW, TSF, AMC, SA and TIBC in group A are shown in *Table 2*. BW increased in 10 patients (71 per cent), decreased in one (7 per cent) and remained unchanged in three patients (21 per cent).

The postoperative modifications of BW, TSF, AMC, SA and TIBC in group B are shown in *Table 3*. BW did not increase in any patient, decreased in six (67 per cent) and remained unchanged in three patients (33 per cent).

Three patients had postprandial diarrhoea in the 2-month postoperative period without other signs of dumping syndrome. Neither dysphagia nor vomiting were prominent complaints.

Discussion

A sharp weight loss was often described after TG and was regarded as an inevitable consequence of the operative procedure[1–3,14]. Bacterial overgrowth, relative pancreatic enzyme insufficiency, mucosal lesions of the small intestine and shortened small intestinal transit time were advocated by several authors as possible causes of this postoperative malnutrition[2,5–10,15]. However, Lawrence *et al.*[16] were unable to find any significant correlation between body weight and nitrogen and fat malabsorption.

Several other workers suggested that the major cause of weight loss after TG might be inadequate calorie intake[6,17–19]. Roberts *et al.*[20] reported that only three of the twenty gastrectomized patients studied had energy intakes greater than

Table 2 *Variations of nutritional parameters in the 14 group A patients, who reached recommended dietary allowances on the sixth postoperative month*

Patient no.	Body weight (kg)		Serum albumin (g/dl)		Total iron binding capacity (μg/dl)		Arm muscular circumference (cm)		Triceps skin fold (mm)	
	1st*	6th†	1st	6th	1st	6th	1st	6th	1st	6th
1	69	69	3·4	4·3	264	358	24·2	24·6	12·4	12·0
2	58	61	2·9	3·5	390	368	24·3	24·9	10·2	10·4
3	36	43	3·7	4·1	182	253	18·4	19·5	13·2	14·4
4	52	53	3·9	3·9	294	308	20·4	20·8	5·8	6·2
5	52	55	3·1	4·0	190	444	20·6	21·5	14·7	16·1
6	50	50	2·6	4·0	182	304	22·1	21·9	6·4	6·8
7	53	57	3·0	3·4	252	246	22·3	23·4	11·4	12·0
8	63	65	2·8	3·8	274	324	24·8	25·4	13·9	14·1
9	63	63	3·3	3·8	186	422	26·8	27·0	10·3	10·2
10	59	62	3·2	3·1	218	298	23·9	24·9	10·7	11·0
11	70	75	3·3	4·3	—	—	24·2	25·3	10·5	11·7
15	40	43	3·8	4·1	300	348	17·4	18·2	10·0	10·4
17	48	46	2·9	3·1	200	270	22·8	22·2	12·1	10·6
22	58	60	3·0	3·8	228	330	21·2	21·8	12·2	11·9
Mean	55·1	57·3	3·2	3·8	243	329	22·4	23·0	11·0	11·3
s.d.	9·9	9·6	0·4	0·4	61	60	2·6	2·5	2·5	2·6
P‡	<0·05		<0·0005		<0·005		<0·001		n.s.	

* first postoperative month
† sixth postoperative month
‡ Student's *t* test for paired data

Table 3 *Variations of nutritional parameters in the nine group B patients, who did not reach recommended dietary allowances on the sixth postoperative month*

Patient no.	Body weight (kg)		Serum albumin (g/dl)		Total iron binding capacity (μg/dl)		Arm muscular circumference (cm)		Triceps skin fold (mm)	
	1st*	6th†	1st	6th	1st	6th	1st	6th	1st	6th
12	60	60	2·9	3·7	252	300	24·4	24·7	10·9	10·5
13	72	72	3·1	3·7	238	269	26·5	26·4	11·2	11·5
14	59	58	3·5	3·6	242	250	24·9	24·6	9·9	8·9
16	76	75	3·8	3·6	258	248	27·1	26·4	22·2	21·0
18	60	57	3·0	3·1	290	250	21·7	21·0	23·3	22·4
19	44	42	3·6	3·5	186	276	17·8	17·4	16·6	15·5
20	42	42	3·1	3·4	134	243	18·8	18·7	6·9	7·4
21	46	44	3·1	3·2	238	240	19·7	18·8	10·4	9·5
23	79	77	3·0	3·2	254	210	22·8	22·4	13·5	13·0
Mean	59·8	58·5	3·2	3·4	232	254	22·6	22·3	13·9	13·3
s.d.	13·8	13·9	0·3	0·2	46	25	3·4	3·5	5·7	5·3
P‡	< 0·01		n.s		n.s.		< 0·01		n.s.	

* first postoperative month

† sixth postoperative month

‡ Student's *t* test for paired data

8·37 MJ per day (2000 kcal). In 1967, Adams[4] confirmed an insufficient average calorie intake after TG, but found that 10·5 per cent of the 182 patients studied regained their pre-illness body weight. Therefore, significant weight gain after TG, although uncommon, was demonstrated to be physiologically possible. This observation was confirmed by Bradley and co-workers[11], who studied 10 patients who had previously undergone TG without evidence of malignancy. In the controlled hospital situation, these patients were able to exceed RDA for calories, carbohydrates, fats and proteins. However, food intake decreased significantly when the patients returned home (calorie intake declined by 29 per cent). The largest decrease was noted to be in the carbohydrate fraction; in fact, after leaving hospital, carbohydrate, fat, and protein intakes declined by 42 per cent, 30 per cent and 7 per cent, respectively.

Possible explanations for inadequate calorie intake after TG include: absence of hunger, dyspepsia due to agastria, alteration of the intestinal motility, early postprandial satiety. For this reason several authors[14,16,21–26] advocated the construction of substitute gastric pouches of jejunum or right colon to increase postoperative food intake.

Pellegrini *et al.*[12] reported that an artificial gastric reservoir is not necessary to ensure a correct food intake after TG. They examined small bowel transit of solid food in 10 patients who had TG with end-to-side Roux-en-Y oesophagojejunostomy reconstruction and compared the transit pattern with that in 5 control subjects. Transit of food through the small intestine is slower in gastrectomized patients than in control subjects and, because the proximal jejunum empties rapidly during the meal, a meal of normal size can be consumed. Nevertheless, several of these gastrectomized patients showed an important weight loss.

In 1986, Cristallo *et al.*[13] noted that malabsorption after TG is not a major clinical problem if an adequate dietary intake is maintained. A mild degree of steatorrhea was observed in four out of twelve patients. The Schilling test (second phase) was abnormal in eight patients, while the oral administration of antibiotics (neomycin) improved the absorption of vitamin B_{12}. Since the jejunal morphology was normal in all patients, the authors explained the occurrence of stearorrhea and the alterations of the second phase of the Schilling test by a bacterial overgrowth in the jejunum, as reported by Tabaqchali *et al.*[8]. Despite this malabsorption, malnutrition was registered in only one patient and its low incidence was explained by the correct dietary regimen observed by the patients after operation.

To obtain an adequate calorie intake dietary re-education is necessary in gastrectomized patients, and a strict nutritional follow-up should be started as soon as possible to avoid a sharp weight loss in the early postoperative course, when the main dietary problems occur. The patients in our study did not have overt evidence of persistent neoplastic disease. They did have a duodenal bypass and no gastric reservoir, because the reconstruction of the alimentary tract was done by end-to-side Roux-en-Y oesophagojejunostomy. Thus, if the duodenal bypass and the absence of a gastric reservoir were important factors in the development of malnutrition, one would expect a high incidence of malnourished patients in our series. In fact, only seven of the twenty-three patients had weight loss in the 6 month postoperative period, and it was never higher than 5 per cent.

In our patients, despite the advice provided during hospitalization and at discharge, the average calorie intake in the first postoperative month was insufficient. In 14 patients (group A) we noted a remarkable improvement of the average calorie intake and RDA was reached at 6 months, while nine patients (group B) failed to reach their RDA. No difference was present in tumour stage between group A and group B. Of the nine group B patients, seven were over 70 years old, while no group A patients was aged 70 years. In our opinion this is probably because the elderly patients could have had more difficulty in getting an adequate nutritional support after total gastrectomy We also observed a significant increase of protein, fat and especially carbohydrate dietary intake, which, as already reported by Bradley *et al.*[11], represents the most variable share in the feeding of the gastrectomized patients. The sharp improvement of the calorie intake observed in the sixth postoperative month could be due to the patients' spontaneous progressive adaptation to their changed anatomy. However, several reports[6,17–19] note that gastrectomized patients become progressively malnourished if they are not controlled with a nutritional follow-up.

The study of the groups A and B further confirmed the strict relation between food intake and nutritional status after TG. In all patients we observed a decrease in BW > 10 per cent with respect to usual body weight at discharge. Therefore, if TG did not seriously compromise digestion and absorption of food, patients who have an adequate calorie intake could increase their BW. In fact, a gain in BW was observed in 10 group A patients, while no increase in BW was observed in group B patients. Moreover, of the seven patients who showed weight loss in the sixth postoperative month, only one was part of the group A. In the 14 group A patients we noted a statistically significant 2 kg average rise in BW in the 6-month postoperative period. This confirms the ability to regain body weight after TG, if an adequate dietary intake is maintained, as reported by Adams[4]. The nine group B patients showed a statistically significant 1 kg average decrease in BW; however, all patients, but one, maintained their pre-operative performance status, evaluated according to the Karnofsky index[27].

In the analysis of the anthropometric parameters, no significant variations of the TSF were observed in either group, while regarding AMC a significant increase was observed in group A and a significant reduction was noted in group B.

We would emphasize the significant increase of SA and TIBC in the group A: the average value was lower than normal for both these visceral proteins in the first postoperative month and above normal in the sixth. In particular, in the sixth postoperative month only three out of fourteen patients showed serum albumin lower than 3·5 g/dl (no patient had SA $<3{\cdot}0$ g/dl) and only one patient had TIBC values lower than 250 μg/dl. The increase of TIBC values observed by comparing first to sixth postoperative month was not due to a decrease of serum iron with time (data not shown). By contrast, four out of the nine group B patients had values of SA and TIBC lower than normal on the sixth postoperative month.

The body weight gain and the improvement of the protein synthesis in the group A patients show that a satisfactory utilization of the dietary substrates is possible in gastrectomized subjects. An adequate food intake in these patients can lead to anabolism with consequent improvement of the nutritional status.

The indications for TG are still discussed. Whatever the opinion on this problem, we think that avoidance of TG because of its metabolic consequences, especially malnutrition, should be abandoned. After TG the ability to feed correctly persists and with an adequate calorie intake patients can reach or maintain a good nutritional status. To obtain this goal patients should undergo a careful nutritional follow-up, which is as important as the oncological follow-up. To evaluate the accuracy of our computer program, we previously checked it in a group of hospitalized patients. We calculated the error with respect to the daily calorie intake as ±10 per cent. This error was attributed to an imperfect form filling by the patients.

In conclusion, malnutrition is not an inevitable consequence of TG and can be prevented by an adequate dietary intake. In fact, a close relationship between calorie intake and postoperative time course of the nutritional parameters was observed. A careful nutritional follow-up and dietary education is necessary after TG, especially in the early postoperative months, when gastrectomized patients have most difficulty taking adequate nutrition.

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Home parenteral nutrition: a review of 100 patient years of treatment in 76 consecutive cases

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Over the last 10 years, the Nutrition Unit at Hope Hospital has trained and looked after 76 patients on home parenteral nutrition for a total of 100 patient years. Although 40 per cent of patients have required home parenteral nutrition for 6 months or less one patient has been on treatment for 7 years. The quality of life measured on a 4 point scale was good for the majority of patients. Sepsis and superior vena caval thrombosis are the main problems encountered. Overall mortality rate was 18 per cent and the sepsis rate was 0·14 episodes per patient per year. Home parenteral nutrition is an effective and safe treatment of intestinal failure.

Keywords: Parenteral nutrition, intestinal failure

Intestinal failure, as defined by Fleming and Remington[1], is 'the reduction in functioning gut mass below the minimal amount necessary for the adequate digestion and absorption of nutrients'. Surgeons will immediately recognize this as a problem that results from high output intestinal fistulae, disorders of intestinal motility such as ileus, the short bowel syndrome and extensive small bowel disease.

In most instances the situation is reversible by restoration of normal motility, adaptation of residual short bowel, closure of fistulae, or remission in the underlying disease. In some patients, however, the loss of absorptive capacity is permanent and long-term nutritional support is essential.

In 1980, a purpose-built unit was opened at Hope Hospital, Salford, for the treatment of an increasing number of patients referred with severe intestinal failure[2]. The unit has developed particular expertise in the management of these cases in general and the safe, prolonged administration of parenteral nutrition in particular. With increasing experience mortality rates have fallen and catheter complications are rare.

In patients with permanent or prolonged intestinal failure long-term parenteral nutrition as a hospital inpatient is unacceptable both for social and economic reasons. Such patients should be considered for parenteral nutrition at home.

For more than a decade, centres in North America and Europe have been administering home parenteral nutrition (HPN)[3–5]. However, in many instances the number of patients in the individual reports has been so small that it has been difficult to assess the overall effectiveness of this type of treatment and the problems associated with it.

All our patients have been entered on the HPN register for the UK and Ireland which last year reported on its first 200 cases[6]. It was possible to come to a number of conclusions based upon analysis of this heterogeneous group. In particular it became clear that those patients in whom intestinal failure was secondary to generalized disease such as atherosclerosis did not fare as well as those in whom it was the result of primary small bowel disease, e.g. Crohn's disease or volvulus In this paper we describe, in greater detail, our own experience of the first 100 patient years of HPN at Hope Hospital.

Patients and methods

Between October 1978 and March 1987, 76 patients were sent home from Hope Hospital on HPN. There were 40 males (mean age 34 years, range 9 months to 61 years) and 36 females (mean age 42 years, range 19–76 years). Fifty-nine of the patients were referred directly to the Nutrition Unit from other hospitals. The majority of the remainder were also tertiary referrals but had been sent to other clinicians within the Salford District before coming to the Nutrition Unit. The clinical details of these patients are summarized in *Table 1*. Crohn's disease was the commonest primary disease (45 per cent of cases) and short bowel syndrome was the commonest postsurgical complication requiring HPN The decision to institute parenteral nutrition was based upon the inability of these patients to maintain normal body weight and chemistry by oral feeding with any form of enteral regimen including elemental and oligopeptide diets, however administered. The decision was always made with the agreement of the medical gastroenterologist who is an integral part of the nutrition team HPN was considered only when sepsis had resolved and when the patient was well enough to go home and yet obviously not able to maintain his nutritional state without prolonged intravenous feeding.

Silicone elastomer catheters are used in all patients to infuse the nutrient solution Broviac catheters were used most frequently (56 per cent), with Hickman catheters being used in 13 per cent (Schuco International London Ltd , UK). Vygon Nutricath catheters (Vygon Ecoun, France) were used in the 28 per cent of cases in which it was judged that HPN would be required for several weeks rather than

Table 1 *Clinical details of the patients who received home parenteral nutrition*

	Complications of that disease					
	Short bowel	Fistula	Exacerbation	Malabsorption	Other	Total
Crohn's disease	21	7	5	1	—	34
Mesenteric vascular disease	10	1	—	—	—	11
Small intestinal volvulus	4	—	—	—	—	4
Radiation enteritis	1	2	—	2	—	5
Pseudo-obstruction	1	—	1	1	—	3
Scleroderma	—	—	1	—	—	1
Polyarteritis nodosa	2	—	—	—	—	2
Other	5*	3†	1‡	4§	3¶	16

*Trauma, ovarian Ca, multiple fistulae, polyposis coli and anastomotic dehiscence; † pancreatic abscess, gastric Ca and oesophageal Ca ‡ coeliac disease; § malabsorption of unknown cause; ¶ neurotensinoma, insulinoma and starch peritonitis

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several months. Two patients had Portacath catheters for intermittent infusion of electrolyte solutions.

Catheters were inserted in the operating theatre by staff from the University Department of Surgery. The Broviac and Hickman catheters were inserted by cutting down on the cephalic vein in the deltopectoral groove. The Vygon Nutricaths were inserted percutaneously into the subclavian vein All were screened into position in the right atrium using an image intensifier, flushed with heparinized saline and locked with 2000 units of heparin The lines were all tunnelled to exit on the anterior chest wall, close to the midline, at a point where the patient could easily see and dress the exit site.

Energy and nitrogen requirements were determined by indirect calorimetry and from measured nitrogen losses. The nutrient solutions, with the exception of lipid emulsion, were mixed in a 3-litre bag and infused with the aid of a volumetric infusion pump (IMED, Abingdon, UK). With the exception of 10 patients, infusions were made during the night. Treatment was instituted and discontinued by the patient who also cared for and dressed the catheter site. Two thousand units of heparin was used to lock the line after discontinuation of the infusion. Sixty patients required infusions every day, with the others requiring from two to five infusions per week.

Training for these procedures was facilitated by tape–slide programmes and videotapes, as well as an illustrated booklet produced by the unit and given to every patient. Training was completed within 2 weeks in 63 per cent of cases Only two patients required training for more than 4 weeks.

Expert advice for patients at home was available 24 h/day from nutrition unit staff and patients were seen regularly at intervals of 1–3 months at the HPN Clinic. Metabolic and nutritional problems necessitating changes in treatment were dealt with at the clinic while minor problems with the lines or pumps were sorted out, on an outpatient basis, in the Nutrition Unit.

Results

Since 1978, there has been a steady increase in the number of new patients being trained for HPN at Hope Hospital. The present rate is equivalent to one patient every 3 weeks (*Table 2*). Altogether, HPN has been administered for a total of 100 patient years with a mean of 16 months per patient (range 2–84). Three patients were transferred back to the referring unit and are therefore discounted from further analysis. In 40 per cent of the patients, HPN was in progress for 6 months or less (*Table 3*) although in nine of these patients, it was still in progress at the end of the study. Twenty-two patients received HPN for 18 months or longer with a maximum of 7 years.

Thirty-five patients carried out their normal full-time occupation while on HPN (*Table 4*) and thirteen were able to work part-time. These patients fall into grades 1 and 2, as previously defined[6], for the quality of life while on HPN. Two schoolboys achieved a total of 19 GCE 'O' level passes while receiving treatment. Four babies were born alive and well to three mothers on HPN[7].

Of the 39 patients in whom HPN was discontinued, it was stopped in 22 when oral nutrition became possible because of intestinal adaptation or fistula closure. Two of these patients subsequently required further courses of HPN. Intestinal adaptation was judged to have occurred when patients developed rapid weight gain during HPN. Its adequacy was tested by weaning the patients off treatment while closely monitoring their nutritional variables, in particular, weight, serum albumin, anthropometry and muscle function studies. In four patients surgery was required before the resumption of oral feeding. Staged surgical procedures with an intervening period of HPN have become an important technique in managing patients with difficult intestinal fistulae[8].

Fourteen patients died while on HPN (*Table 5*). Five of the deaths can be related to HPN, superior vena caval (SVC) thrombosis being responsible for three. One patient died of multiple injuries after a road traffic accident. The other eight patients died of complications of their primary disease.

Twenty-three patients experienced a total of 32 non-fatal complications with the intravenous catheters (*Table 6*). Catheter sepsis indicates that the line was infected but that the patient was not septicaemic. The average time spent in hospital as a result of these complications was 6 days. Infected catheters were always removed. Blocked catheters could sometimes be cleared by a bolus of urokinase and flucloxacillin; otherwise they were removed. With respect to the total time spent on HPN, this is equivalent to one complication every 3·1 patient years. Forty-three patients remained totally free from complications.

Discussion

HPN has been in use in the USA for over 10 years and in this country since 1977. Although a large number of centres in the UK and Ireland have started a total of 235 patients on HPN, only a small number of centres account for most of the patients[6]. The Nutrition Unit at Hope Hospital, Salford, has treated almost a third of this total. Most of the patients have been referred from other hospitals with either a short bowel syndrome, intestinal fistula or severe Crohn's disease.

In our experience, HPN has proved to be a remarkably safe treatment for patients with intestinal failure. In such severely ill patients, a mortality rate of 18 per cent is not excessive. A catheter complication rate of one complication every 3·1 patient years is also acceptably low.

HPN is expensive, costing approximately £75 per day, but it is far more economical than keeping the patient in hospital. It is

Table 2 *Number of patients commencing home parenteral nutrition each year*

	Year									
	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987
No. starting on HPN	1	4	2	5	6	15	5	17	16	5

HPN, home parenteral nutrition. The figures for 1987 are for only the first 3 months

Table 4 *Patients who performed full-time work while on home parenteral nutrition*

Housewife	13
Able to work but unemployed	6
Schoolboy	3
Student	3
Secretary	2
Shipping manager	1
Cashier	1
Shopkeeper	1
Engineer	1
Joiner	1
Businessman	1
Teacher	1
Architect	1

Table 3 *Length of time patients have been on home parenteral nutrition*

	Length of time (months)													
	0–6	6–12	12–18	18–24	24–30	30–36	36–42	42–48	48–54	54–60	60–66	66–72	72–78	78–84
Total no.	31	7	16	4	5	3	4	2	2	0	0	0	1	1
No who have completed	22	4	9	2	1	0	1	0	0	0	0	0	0	0

Table 5 *The patients who died while on home parenteral nutrition*

Age	Sex	Diagnosis	Cause of death
20	M	Pseudo-obstruction	Road traffic accident
76	F	Mesenteric vascular disease	Bronchopneumonia
54	M	Scleroderma	Exacerbation of disease
54	M	Pancreatic abscess	Recurrent pancreatic abscess
26	M	Neurotensinoma	Recurrence of disease
36	F	Crohn's disease	Renal failure
45	F	Crohn's disease	Carcinomatosis
12	M	Malabsorption	SVC thrombosis
41	F	Coeliac disease	Torrential gastrointestinal bleeding
21	M	Malabsorption	Endocarditis and bronchopneumonia
6	M	Food allergy	SVC thrombosis
38	F	Crohn's disease	SVC thrombosis
35	M	Radiation enteritis	Septicaemia
68	F	Crohn's disease	Pancreatitis and bronchopneumonia

SVC, superior vena caval

Table 6 *Catheter complications*

Sepsis	
Systemic	7
Catheter	7
Mechanical	
Blockage	12
Displaced	3
SVC thrombosis	3

SVC, superior vena caval

also better for the morale of patients if they can be returned to home and work. Half our patients required HPN for less than a year before their bowel adapted or their fistula closed, following which they returned to normal feeding. There seems little need to justify HPN in such cases. Most of the others have the short bowel syndrome and require long-term HPN. However, many of these patients can return to work and live relatively normal lives while on treatment. It would be difficult to deny such patients a treatment which restores their independence. Twenty-one of our patients have been on HPN for more than 2 years.

Sepsis used to be the major problem in patients on HPN. The advent of specialized units and multidisciplinary teams under surgical control and the implementation of strict nursing protocols for central line care has led to a major reduction in the incidence of sepsis. Our rate of sepsis is 0·14 episodes per patient year which compares well with the best of the USA series[9,10] and is significantly better than the overall UK rate (0·35 per patient per year; $P<0{\cdot}001$).

The results in our series compare well with similar series from the USA. In 1984 Dudrick *et al.* described their experience of 100 patient years of HPN in a 10-year period. The patients were similar to ours in age, sex and disease. Their overall complication rate of one complication every 1·2 patient years and their sepsis rate of 0·38 episodes per patient per year are worse than ours. However, four immunosuppressed patients distorted their figures and, without these, their figures are similar to ours.

Indwelling catheters are by no means free of complications and SVC thrombosis arising in the long-term patients is now our major concern. Three of the six patients who developed SVC thrombosis died of pulmonary emboli while on HPN. There is no obvious reason why these six should have developed SVC thrombosis. Two were children. Two had Hickman catheters and the other four had Broviac catheters. None had percutaneous insertion of their catheters, which has been implicated as a cause of caval thrombosis. Three of the six had had an episode of sepsis at some stage prior to the development of the thrombosis which occurred at intervals of 3 months to 6 years after insertion of the catheter. All patients had had heparin 1000 units/l added to their big bags. This has recently been increased to 3000 units/l.

HPN is to be recommended in the treatment of patients with acute or chronic intestinal failure. As with any other specialized area of medicine the best results occur where there is a constant supply of patients who need treatment so that problems and complications will be recognized early and averted. In such circumstances the patients will be well trained in the techniques required. We believe that HPN is a treatment best managed in specialized units by teams led by surgeons who are able to deal not only with the nutritional problems but also with the wide spectrum of disease that occurs in these patients, particularly abdominal sepsis and intestinal obstruction.

We consider our results show that the availability of a dedicated unit has helped us achieve low mortality and morbidity rates by encouraging the team approach which is so necessary for success. The presence of the unit has facilitated the training as well as the nutritional and metabolic management of both inpatients and home patients and has ensured the continuity of care so important for achieving success in these difficult but interesting patients. We recommend that similar units be established on a regional or supraregional basis.

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Appraisal of a tissue glue in the treatment of persistent perineal sinus

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Between 26 and 37 per cent of patients having proctectomy for inflammatory bowel disease, particularly Crohn's disease, will develop a persistent perineal sinus[1–3]. Treatment may range from simple pad wearing to major flap surgery[4,5]. Even the commonest simple treatment, currettage and laying open, may involve hospitalization and prolonged follow-up.

A new sealant (Tisseel, Immuno Ltd.) is claimed to have an 80 per cent success rate in managing persistent sinuses[6]. As it can be used as an out-patient treatment it has obvious economic advantages over operative treatment.

In the last 3 years we have assessed the use of the sealant in a series of 13 patients with persistent sinus following proctectomy.

Patients and methods

Methods

Pretreatment investigation includes detailed review of the past history and operative findings to exclude residual foreign bodies, tumour or mucous membrane. A bacteriological culture is taken with a swab and a sinogram outlines the size, extent and complexity of the sinus. In order to assess the efficacy of the treatment, all patients with a persistent sinus were treated during this period.

The patients had the technique explained, and consent was obtained. The patient lay in the left lateral position with the left buttock elevated on a cushion and the sinus exposed. A soft plastic 'filling tube' (3 mm diameter) was inserted into the sinus. An antibiotic solution, to which the flora of the sinus was sensitive, was instilled into the sinus. The volume of the sinus was estimated from the X-ray and recorded as the volume of antibiotic solution instilled before leakage occurred. The patient was now ready for instillation of the sealant.

The sealant comes as a two-component system in special packs of different volumes (1, 2, 5 ml which make up to 2, 4 and 10 ml respectively). The appropriate volume is chosen to match the capacity of the track. The sealant is produced from pooled human plasma; it is a biological system and has to be mixed at 37°C, for which a special mixing heater is available from the company. The components are available in a pack as four containers: lyophilized fibrinogen, aprotinin solution (3000 k units/ml), lyophilized thrombin, and calcium chloride (40 mmol/l).

After warming to 37°C in the customized warmer, the fibrinogen and the aprotinin are mixed, and the thrombin and the calcium chloride are mixed. The two solutions must be kept separate and at 37°C. On completion of mixing (about 8–10 min) the components are drawn up into separate syringes of appropriate size. A Y connector, ensuring simultaneous emptying of the syringes, is supplied with the kit. The components are then fitted to the filling tube in the sinus and simultaneously emptied as the tube is withdrawn to ensure complete filling of the cavity (*Figure 1*).

The kit contains two hardeners, one which completes within a few seconds, and another which takes up to 10 min. We used the quick setting component almost exclusively. The patients were provided with a small pad and allowed home immediately and instructed to return in six weeks, or sooner if problems arose.

The manufacturers supply the following warning when supplying the sealant:

> 'Lyophilized heat treated Tisseel is exclusively manufactured from the plasma of European donors who are tested at every donation for HBsAg, anti-HIV and alanine aminotransferase levels. Donors with HBs antigenaemia, anti-HIV or with elevated ALT levels are irrevocably excluded from the plasmapheresis programme. The final product is again tested for the absence of HBsAg. As an additional precaution, lyophilized Tisseel is subjected to product specific heat treatment at 60°C for 30 h. This method has been shown to be effective in reducing the HIV titre by 10^6 or more infectious units per millilitre.
>
> Following several clinical studies and the extensive use of Tisseel no evidence of an increased risk of transmitting viral hepatitis has been shown. Despite this evidence and the precautions taken in selection of donors together with the inclusion of a heat treatment step during production, the risk of transmission of viral hepatitis cannot be excluded with absolute certainty.'

Patients

Thirteen patients were assessed. Clinical details are shown in *Table 1*. Six patients had proctectomy for ulcerative colitis, four for Crohn's disease, and three for cancer. The mean time following operation was 34 months (range 15–132 months since proctectomy). Previous attempts to close the sinus in the group ranged from none to four revisions (mean 2·2). Two patients had been turned down as candidates for further surgery because of major cardiac or respiratory insufficiency.

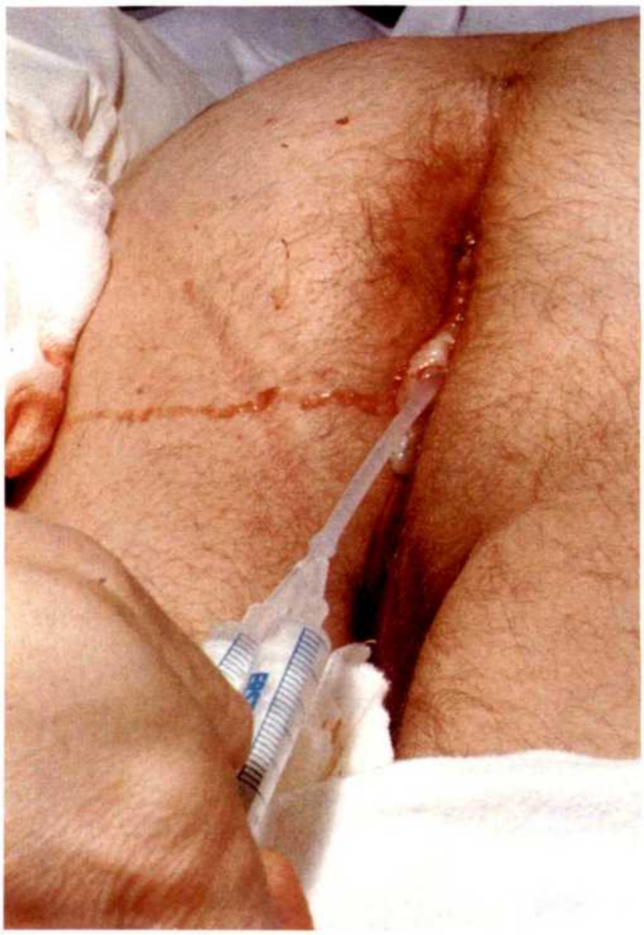

Figure 1 *The instillation of tissue glue*

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Table 1 *Patient details*

Patient no.	Sex	Age (years)	Date of Tisseel	Disease	Operation	Date of operation	Sinus volume (cm^3)	Bacteriology	Contraindications	Previous attempts	Attempts	Final result	Residual volume	Follow-up* (months)
1	F	57	22/12/83	UC	PPC	1982	6	*S. epidermidis*	MI	3	1	Improved	1	37
2	M	63	12/12/83	UC	PPC	1982	12	*S. epidermidis*	MI	1	1	Healed	—	37
3	M	51	17/01/84	Ca	A–P	1982	4	*S. epidermidis*	—	3	1	Healed	—	36
4	M	34	20/01/84	UC	PPC	1973	1·2	*S. epidermidis*, diphtheroids	—	4	3	Improved	1	36
5	F	57	28/02/84	CD	PPC	1981	14	*S. epidermidis*, *Peptostreptococcus*	Enteroperineal fistula					
6	M	22	29/02/84	CD	PPC	1982	2	*S. epidermidis*, enterococci	Enteroperineal fistula					
7	M	28	10/07/84	CD	PPC	1982	30	Enterococci	—	2	2	Unchanged	—	29
8	M	74	17/08/84	Ca	A–P	1983	6	Enterococci, bacteroides, peptostreptococci, *S. albus*	—	0	1	Healed	—	28
9	M	50	20/12/85	CD	Proct	1983	8	No growth	—	2	2	Healed	—	13
10	M	34	18/03/86	UC	PPC	1981	48	*S. epidermidis*	—	4	2	Unchanged	—	10
11	F	30	18/04/86	UC	PPC	1985	5	No growth	—	1	2	Healed	—	9
12	F	53	22/05/86	UC	PPC	1984	7	*S. epidermidis*	—	4	3	Improved	2	8
13	M	75	17/10/86	Ca	A–P	1984	4	Diphtheroids	—	0	1	Improved	1	3

UC, ulcerative colitis; CD, Crohn's disease; Ca, carcinoma rectum; PPC, panproctocolectomy; A–P, abdominoperineal excision; Proct, proctocolectomy; MI, myocardial infarction; * time since instillation of tissue glue. *S. epidermidis*, *Staphylococcus epidermidis*; *S. albus*, *Staphylococcus albus*

Results

The table shows the initial bacteriology of the sinus track. In two patients the sinus swab was reported as showing no growth. The majority of the others showed *Staphylococcus epidermidis*.

Shortly after instillation of the sealant it became obvious that two of the patients had enteroperineal fistulae, because of an increase in discharge which became offensive. In each of these the sinogram had been unable to detect the presence of a fistula, nor had bacteriology suggested an enteric communication (cases 5 and 6). In both patients Crohn's disease was the underlying pathology and disease activity indices were within normal limits.

Of the other 11 patients, 5 healed completely, although 2 of these required 2 attempts at sealing. Their sinuses have not recurred in 129 patient months of follow-up.

Four of the sinuses have subjectively improved in the patients' assessment. Two of these are now so small as to require no further dressings or pads; nevertheless a small sinus remains. The other two have become smaller during the course of treatment and despite three instillations have not completely healed.

Two have remained unchanged after two attempts at sealing.

Discussion

The unhealed perineal sinus remains a problem, especially after proctectomy for inflammatory bowel disease[2,3]. Many of the patients will be unfit or unwilling to have further surgery. While many procedures are available to repair the defect[4,5], simple methods should be tried in the first instance. Initial investigation of the patient should include sinography in an attempt to exclude the presence of an enteroperineal fistula, as well as to delineate the size and ramifications of the sinus. In our two cases who had fistulae the initial bacteriology and the X-rays were unhelpful. Following instillation of the sealant, they both developed wet, smelly perineal wounds, and both subsequently were treated surgically. Most of the sinuses contained skin bacteria, while four contained flora consistent with perineal contamination. The ideal sinus for this procedure is the long thin track with few side arms. Patients 7 and 10, whose sinuses remained unchanged, had large spherical cavities and would probably have been best treated by initial laying open to create a smaller track, or by muscle graft[5]. All patients were treated as out-patients without problem, except one patient who lived some way from the hospital and could not travel.

Our results were unfortunately less good than a previous study[6]. At least two of the sinuses were large and probably unsuitable for this technique. We do not believe that the sealant contributed in any way to the formation of the two fistulae. In view of the simplicity of the procedure and its low morbidity, it should be tried in all cases of persistent sinus before embarking on major surgical procedures.

Acknowledgements

We should like to thank the company Immuno Ltd. (Arctic House, Rye Lane, Dunton Green, Sevenoaks, Kent TN14 5HB, UK) for providing the Tisseel, and for their technical help and advice. We should like to thank the clinicians who allowed us to study their patients, Professor M. Keighley, Mr J. Temple, Mr J. Fielding, Mr T. V. Taylor, and Mr J. D. Hamer.

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Experience with pancreatic banding: results of a simple technique for dealing with the pancreatic remnant after distal partial pancreatectomy

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The main complications after partial pancreatectomy (distal, hemi-, subtotal) are the development of pancreatic fistula and abscess formation. The reported incidence of pancreatic fistula after partial pancreatic resections varies from 6 to 30 per cent, depending on the nature of the underlying disease and the method of dealing with the residual pancreas[1-5]. The average reported incidence of postoperative pancreatic fistula in a collective review of 234 distal pancreatic resections with suture closure of the proximal gland was 13 per cent[1]. Postoperative intra-abdominal abscess formation after pancreatic resection is mainly encountered after resection for pancreatic trauma when there are associated injuries to other organs[4,6-8].

Several techniques have been reported for dealing with the pancreatic remnant. The classical method consists of suture ligation of the pancreatic duct followed by mattress or figure of eight suture closure of the stump. Non-absorbable sutures are necessary because of the rapid digestion of polyglycolic acid and catgut by the pancreatic juice[9]. The Leger's technique[10] of drainage into a Roux-en-Y loop of jejunum is not used frequently unless there is disease or injury to the proximal pancreas or duct[4,6,7]. Otherwise, the procedure adds considerably to the operating time and increases the risk of complications[3,8]. More recently, stapling (TA-55, 4·8 mm staple size, Auto Suture Co., UK) of the pancreatic remnant with or without suture ligation of the pancreatic duct has been reported and shown to be accompanied by a low postoperative morbidity[1,2,11,12].

We have used a simple technique of pancreatic ligature referred to as 'pancreatic banding' over the past 15 years and this paper reports the outcome of our experience with this method of dealing with the pancreatic remnant.

Patients and methods

Technique

The pancreas is first mobilized from the retroperitoneum. The splenic artery is ligated 2·0 cm proximal to the proposed line of pancreatic transection. A 3·0 cm length of the splenic vein is next mobilized from the back of the pancreas and the vein then ligated at either end. Using double 1/0 non-absorbable (black silk) encircling ligatures, the pancreatic parenchyma is tied to compress it sufficiently tightly on either side of the proposed transection to achieve complete haemostasis but without cutting into the pancreatic substance (*Figure 1*). The pancreas is then transected between the encircling ligatures (*Figure 2*). As a result of the complete haemostasis, the pancreatic duct is easily identified and is suture ligated with a 4/0 non-absorbable atraumatic suture (*Figure 3*). The raw surface of the pancreas is then covered with adjacent fat from the transverse mesocolon. A silicone tube drain connected to a closed system is inserted down to the pancreatic stump. More recently, Vicryl bands (Ethicon Ltd, UK) have been used to compress the pancreas as they are less likely to cut into the pancreatic parenchyma and are slowly biodegradable.

Patients

Pancreatic banding has been used in 23 patients undergoing resection for pancreatic disease and 50 patients having an R2/3 radical gastrectomy for gastric cancer (*Table 1*). The pancreas was invaded by tumour in eight of these patients. A hemipancreatectomy was performed in 10 patients and 63 had distal 75 per cent resections (at junction of neck with body). The age range of the entire series was 25–78, median 66 years.

Results

There were two postoperative deaths in the pancreatic group (pulmonary embolism, postoperative haemorrhage due to slipped ligature of the splenic vein) and three deaths in patients after radical gastrectomy (anastomotic leakage from oesophagojejunal anastomosis in two and aspiration pneumonia/adult respiratory distress syndrome in one). The incidence of postoperative pancreatic fistula and intra-abdominal abscess is shown in *Table 2*. All the four fistulae were

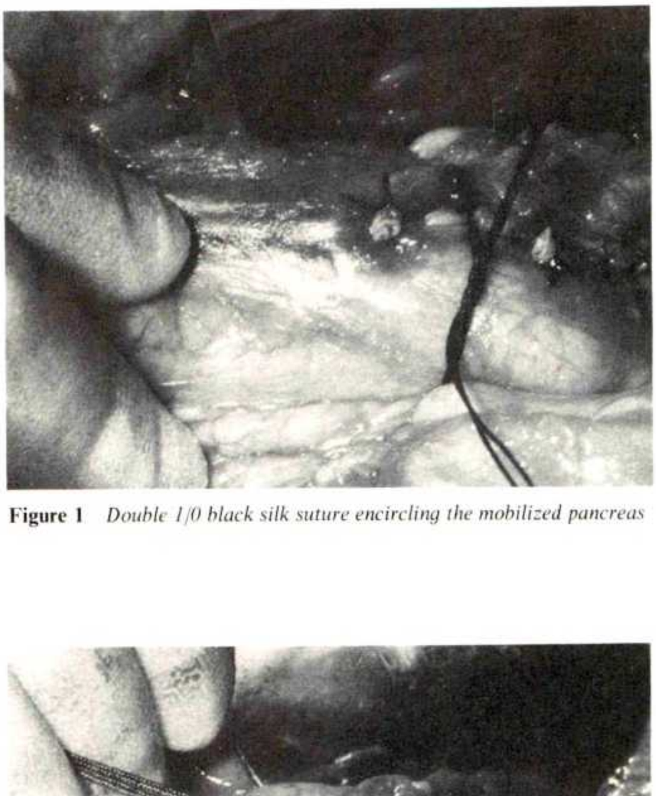

Figure 1 *Double 1/0 black silk suture encircling the mobilized pancreas*

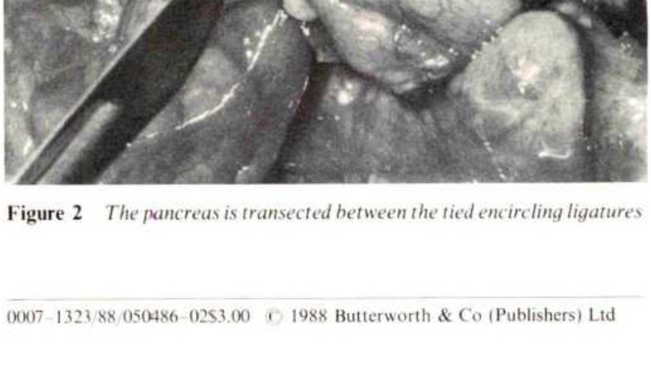

Figure 2 *The pancreas is transected between the tied encircling ligatures*

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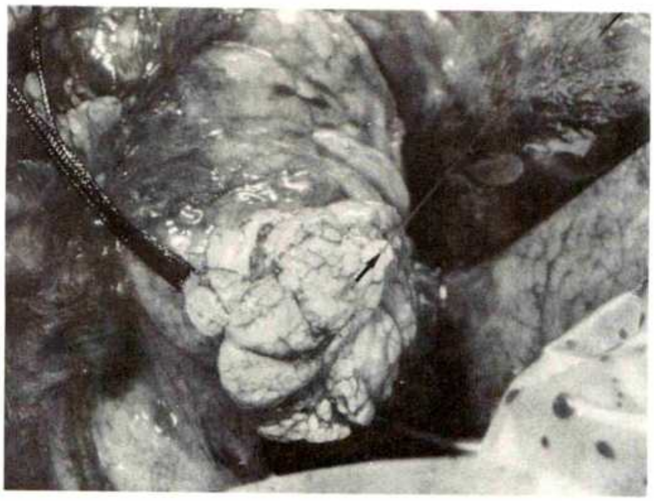

Figure 3 *As a result of the complete haemostasis, the pancreatic duct is easily identified within the cut pancreatic parenchyma and is suture ligated with a 4/0 non-absorbable atraumatic suture*

Table 1 *Details of patients undergoing partial pancreatectomy with banding*

Pathology	*n*	Age (years)
Pancreatic trauma	3	25, 30, 60
Chronic pancreatitis	18	41–62
Pancreatic cystadenoma	1	50
Cystadenocarcinoma of the pancreas	1	58
Radical gastrectomy		
Normal pancreas	42	32–78
Neoplastic invasion of pancreas	8	57–74

Table 2 *Outcome of pancreatic banding*

Outcome	Pancreatic	Gastric	Total
Postoperative death	2/23 (9)	3/50 (6)	5/73 (7)
Fistula	2/23 (9)	2/50 (4)	4/73 (6)
Abscess	0	1/50 (2)	1/73 (1)

Figures in parentheses are percentages

external along the drain tract and consisted of clear pancreatic juice. They all dried up with conservative management within 12 days and were not accompanied by an excoriation of the skin. Pancreatic fistula developed in one patient after subtotal resection for chronic pancreatitis, in another patient who had sustained blunt abdominal trauma to the pancreas and in two patients undergoing radical resection for gastric cancer. The latter two patients had invasion of the pancreas by tumour although review of the pathology showed no tumour at the site of pancreatic transection.

The only instance of intra-abdominal abscess was encountered in a patient who leaked from an oesophagojejunal anastomosis and who eventually died of uncontrolled sepsis. At post mortem, the pancreatic remnant was shown to be intact and not directly responsible for the abscess.

Discussion

In our experience simple banding of the pancreas with encircling ligatures together with suture ligation of the pancreatic duct is a simple and safe procedure with a lower incidence of pancreatic complications than that generally reported in the literature using conventional suture closure[1,2,5]. In addition, the technique ensures complete haemostasis of the cut pancreatic parenchyma and therefore facilitates identification and closure of the pancreatic duct.

There has been an increasing tendency to use staple closure of the pancreatic remnant in recent years[1,2,11,12] following the initial report by Patcher *et al.*[1]. Staple closure is particularly useful when the pancreatic duct cannot be positively identified. The majority of reports on pancreatic stapling have included small numbers and, to date, there have been a total of 68 pancreatic stapled resections reported with an average complication rate of 10 per cent[11]. In a series of 56 distal pancreatic resections there was no observed difference in the postoperative complication rate between stapled and sutured pancreatic remnants. However, this report indicated that staple closure is safer in those patients in whom pancreatic duct closure is not performed[2].

The fistula rate encountered in the present study in the gastric cancer group (4 per cent) can be compared to that reported in a large series of 108 distal pancreatectomies for gastric and retroperitoneal tumours which used mattress closure with or without duct ligation in 102 patients and stapled closure in 6 (reference 5). This study showed a postoperative fistula rate of 10 per cent.

It appears that pancreatic banding is accompanied by a lower postoperative complication rate than that reported by existing techniques and we recommend its general use after partial pancreatic resection provided proximal ductal obstructive disease is excluded.

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Surgical workshops

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Partial splenectomy for splenic cysts

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Non-parasitic cysts of the spleen are rare—fewer than 600 cases have been reported in the world literature. It is thought that they usually develop as a result of spontaneous or traumatic subcapsular haemorrhage of the spleen with subsequent organization and liquefaction. Given the more conservative modern attitude to the management of splenic trauma it is possible that post-traumatic cysts of the spleen will be encountered more frequently. This report of two recent cases of non-parasitic splenic cysts describes a technique for partial splenectomy.

Both patients were women (48 and 57 years) and presented with a history of left hypochondrial pain of 1–2 years duration. Neither had a history of abdominal or thoracic trauma. The spleen was palpable in both patients, and the splenic cyst was diagnosed by ultrasound. In both cases laparotomy revealed a large tense spherical cyst confined to the upper pole of the spleen and partial splenectomy was performed with preservation of the lower pole.

Through an extended transverse incision, the spleen was mobilized and delivered from the abdomen. The hilar vessels supplying the upper pole were divided using fine silk ligatures. It is known that intrasplenic vessels are segmental and largely without intersegmental communication; this allows the spleen to be dissected along planes radiating from the hilum. Although branches of the splenic artery are highly variable, bifurcation outside the spleen is usual. Thus vascular control of the individual poles can be obtained and segments separated along relatively avascular planes.

After devascularization, a line of ischaemic demarcation became evident. A Balasegaram clamp was placed across the spleen along the demarcation line (*Figure 1*) and the upper pole was resected. Failure of the clamp to control haemostasis completely (one case) was resolved by placing a vascular clamp carefully across the remaining hilar vessels. Chromic catgut sutures on blunt-pointed (liver) needles were placed through the splenic tissue. The clamp was then removed and the sutures tied over a roll of collagen haemostatic felt (Collastypt, B. Braun, Melsungen, FRG) (*Figure 2*). The vascular clamp controlling the hilar vessels was then released. There was no bleeding in either case, but suction drains were placed adjacent to the splenic remnant and removed 2 days later. Postoperative recovery was uneventful with complete relief of abdominal discomfort. Histology showed simple unilocular pseudocysts measuring 16 and 18 cm in maximum diameter containing brown turbid fluid. The appearances suggested that the 'cysts' arose as a consequence of subcapsular haemorrhage. At follow-up more than 6 months after operation normal splenic uptake of technetium pertechnate was observed, and there was no evidence of splenic malfunction or peripheral blood films.

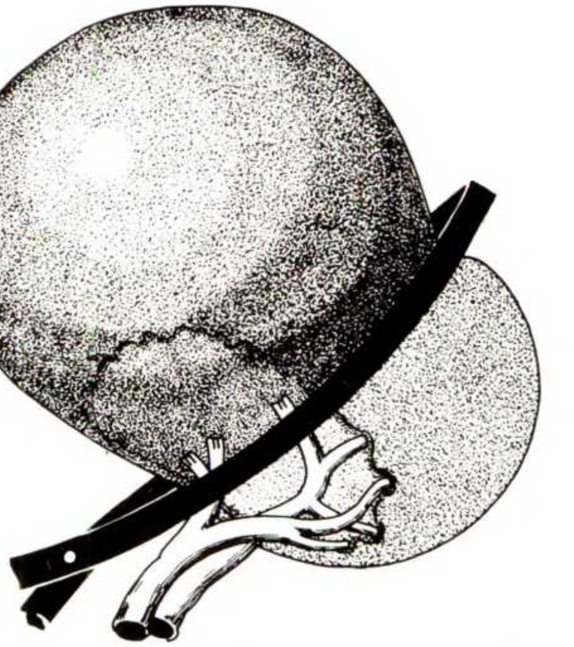

Figure 1 *After dividing hilar branches to the upper pole, a Balasegaram clamp (Downs Surgical plc, UK) is placed across the spleen at the line of demarcation between normal and devascularized tissue*

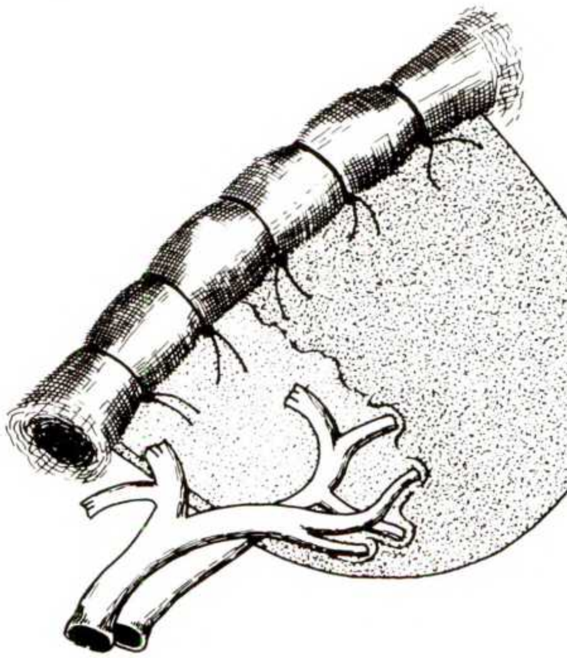

Figure 2 *Catgut sutures secured around a roll of bovine collagen to prevent bleeding from the cut edge of the spleen*

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Case reports

Br. J. Surg. 1988, Vol. 75, May,
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Dieulafoy's erosion in the stomach as a result of an intra-abdominal vascular anomaly

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A patient with massive recurrent gastric bleeding resulting from erosion of an abnormally large hyperplastic artery in the gastric submucosa is reported. This lesion, first described in 1884 by Gallard[1] is better known as Dieulafoy's erosion and was reported by him in 1896[2]. Since then over 100 cases have been reported in the literature under a variety of names[3].

Case report

A 50-year-old Turkish man was admitted with sudden onset of haematemesis. He complained of a vague pain in the upper abdomen that was not related to meals. His medical history, as far as it could be ascertained, was without evidence of previous disease. Physical examination was entirely negative except for a mild tenderness in the upper abdomen.

At gastroscopy it was found that the bleeding originated in the stomach, possibly from a Mallory–Weiss tear.

By the fourth day he had received a total of 18 units of blood. A second endoscopy was unhelpful and an exploratory laparotomy was therefore deemed necessary.

The distal part of the small intestine and the entire colon were filled with blood. Along the margin of the transverse colon a very large and tortuous artery was observed. An arterial arcade appeared to anastomose the vascular beds of the superior and inferior mesenteric artery in which blood flowed in a cranial direction. The elasticity of the vessel wall was preserved and there were no signs of a general arteriosclerosis. Between the spleen and the stomach, along the vasa brevia, a similar enlarged vessel was present. A high gastrotomy was performed and after removal of blood clots a tiny superficial mucosal erosion was noted. Here an abnormally large artery had eroded the mucosa, the top of which showed a defect that was capped by a blood clot. No other mucosal defects or bleeding sites were discovered. A small wedge resection was performed and the vessel was ligated. There has been no recurrence of the haemorrhage since then.

Histological examination of the artery from the bleeding site showed changes compatible with hyperplasia as a consequence of the increased bloodflow in an anastomotic network.

Angiography was performed after surgery using the Seldinger technique. The aorta was elongated. The coeliac and superior mesenteric arteries were occluded at the orifice.

A collateral pathway was visualized arising from the inferior mesenteric artery and taking its course via a huge and very tortuous marginal artery of Drummond. The superior mesenteric artery was filled via this network (*Figure 1*). Another collateral system comprising the left phrenic artery and possibly the left gastric artery also provided blood to the branches of the coeliac artery.

Discussion

The lesions of Dieulafoy's gastric erosion consist of a small mucosal defect of 2–5 mm diameter with minimal inflammatory reaction that is usually located high in the fundus at the lesser curvature, although cases have been reported elsewhere in the stomach[4] and in the jejunum[5,6]. Through this defect a solitary and abnormally large and tortuous artery protrudes, the end of which has become necrotic due to peptic digestion, resulting in rupture and bleeding. It is assumed that the large calibre of the vessel causes compression atrophy of the overlying mucosa. There are no signs of peptic ulceration in the gastric mucosa, neither does the artery show changes of vasculitis or arteriosclerosis.

Associated vascular anomalies elsewhere in the gastrointestinal tract are usually absent. The vessel has the typical structure of a large muscular artery and a regular calibre throughout its often tortuous course in the submucosa[6,7]. The lesion is probably not rare, Velthuyzen van Zanten *et al.*[3] recently described 6 patients and reviewed 101 cases from the literature.

The clinical features have been extensively reported in previous publications. The lesions may occur at any age; a male predominance has been noted. The family history is negative and there are no previous complaints of abdominal pain. Emergency X-ray and even endoscopic examination of the stomach may prove disappointing diagnostic tools as the mucosal lesion is tiny and massive bleeding obscures the site of haemorrhage. This is best demonstrated by visceral angiography unless bleeding has stopped.

The presence of arterial branches in the gastric submucosa that are abnormally large in relation to their location, has been explained by Voth[8] as follows. Normally there is a gradual reduction in the size of arterial branches in the course of the artery through the gastric wall as a result of successive bifurcations. When this branching pattern is absent, unusually large sized arteries may reach the submucosa—the so-called 'calibre persistent artery'. Barlow *et al.*[9] have shown that submucosal arteries along the lesser curvature arise directly from the left gastric artery outside the stomach wall and not from a submucosal plexus, as is the case in other parts of the stomach. Moreover, submucosal arteries have a larger calibre in corpus and fundus than in the antrum (Wanke[10]). This probably explains the frequency of occurrence of persistent calibre type arteries in the upper part of the stomach along the lesser curvature, but not the actual cause of their development.

Our case illustrates that a specific causative factor i.e. the increased bloodflow in a collateral arterial network in the

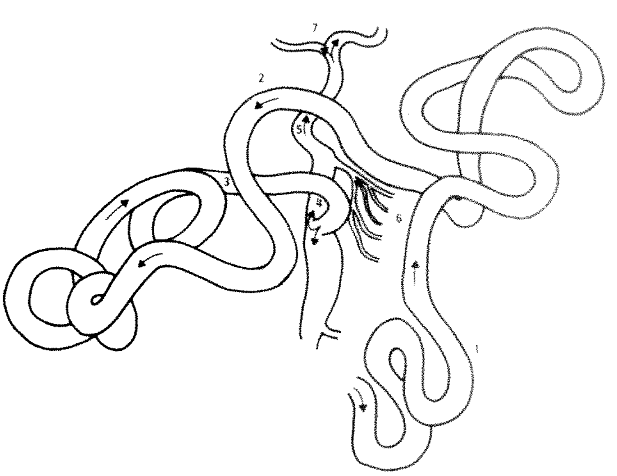

Figure 1 *Schematic drawing of the extensive collateral pathway displayed by angiography.* 1, *Arteria colica sinistra;* 2, *marginal artery;* 3, *arteria colica media;* 4, *arteria mesenterica superior;* 5, *Arc of Bühler;* 6, *jejunal branches;* 7, *coelic branches*

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presence of occlusion of large splanchnic arteries may play a role in the pathogenesis of Dieulafoy's erosion. In our opinion the unusually large calibre of the perforating artery was the result of the altered bloodflow in the epigastrium, which developed secondary to the occlusion of the ostia of both the coeliac artery and the arteria mesenterica superior. Such occlusions are regularly discovered at angiography or autopsy in patients who have never shown symptoms of intestinal angina (Marston[11]).

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Duodenal diverticula and jaundice: percutaneous transhepatic cholangiography may be misleading

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Duodenal diverticula are reported as a rare cause of obstructive jaundice[1–4]. We report two patients with such diverticula in whom percutaneous transhepatic cholangiography (PTC) wrongly suggested the presence of a periampullary tumour.

Case reports

Case 1

An 81-year-old woman admitted in 1982 as an emergency with a 2-day history of severe epigastric and right hypochondrial pain developed obstructive jaundice (serum bilirubin 140 μmol/l, alkaline phosphatase 1260 units/l) during admission. Ultrasonic scanning failed to outline the extrahepatic biliary tree clearly. PTC showed dilatation of both intrahepatic and extrahepatic biliary tract (maximum diameter 16 mm) with delay in the passage of contrast into the duodenum. An area of irregularity and deformity of the duodenum was noted at the papilla of Vater and the appearances were reported as strongly suggestive of an ampullary tumour (*Figure 1*). At endoscopy, using a side viewing duodenoscope, no periampullary tumour was seen and the deformity was attributed to the opening of the common bile duct into a small duodenal diverticulum. She underwent elective choledochoduodenostomy and cholecystectomy 2 weeks after PTC in view of her unrelieved jaundice. Stones were not identified in the biliary tree or gallbladder, but histological examination revealed chronic cholecystitis; open biopsy from the periampullary area showed inflammation only. She made a good recovery and has remained well at follow-up in July 1986.

Case 2

A 71-year-old man was admitted in 1984 as an emergency because of severe epigastric pain of 12 h duration.

Ultrasonic scanning showed a large gallbladder containing thick debris; the extrahepatic tree was not visualized. A diagnosis of acute cholecystitis was made but within a day of admission he developed obstructive jaundice (maximum serum bilirubin 96 μmol/l, alkaline phosphatase 1230 units/l) and PTC 3 days later showed slight dilatation of the intrahepatic and extrahepatic biliary tree (maximum diameter 15 mm). The lower end of the common bile duct was irregularly narrowed and opened into a diverticulum containing a filling defect. The appearance was reported as very suggestive of an ampullary tumour (*Figure 2*). At endoscopy, using a side viewing duodenoscope, no periampullary tumour was seen and biopsy from the area of the papilla of Vater within the duodenal diverticulum showed inflammatory changes only. Cannulation of the papilla of Vater proved impossible

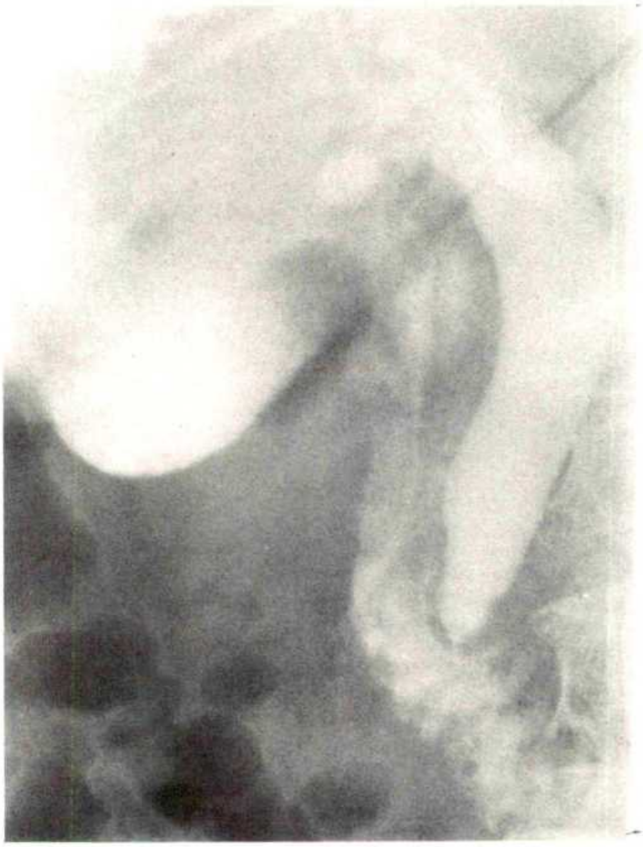

Figure 1 *Percutaneous transhepatic cholangiogram in patient 1 showing dilatation of the common bile duct and an apparent rounded deformity of the medial wall of the second part of the duodenum*

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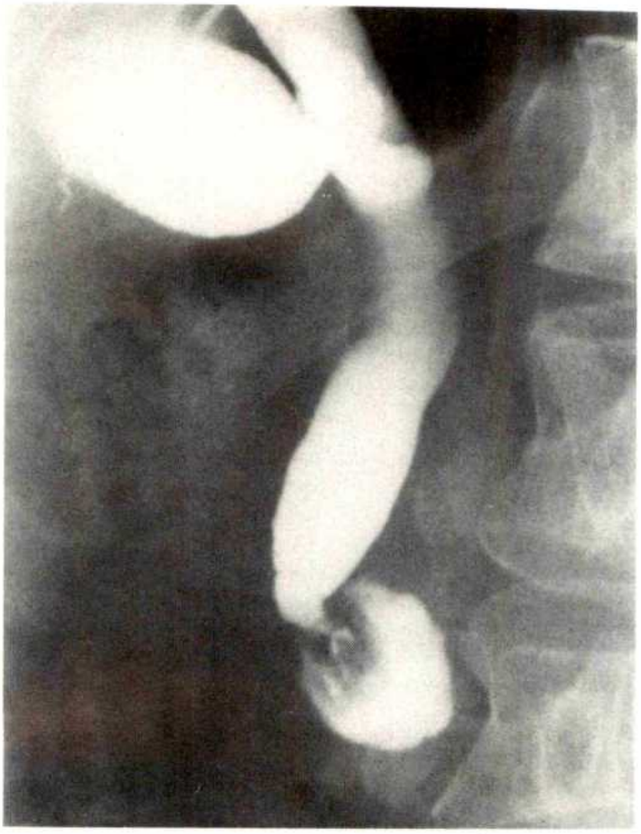

Figure 2 *Percutaneous transhepatic cholangiogram in patient 2 showing a distended common bile duct with an apparent filling defect within an associated duodenal diverticulum*

because of difficulty of gaining access to the papilla within the diverticulum. At laparotomy, 4 days after the PTC, duodenostomy was performed because of the PTC appearances, but no stone or tumour was seen. The duodenum was closed without sphincterotomy and a large gallbladder was removed which showed acute inflammation with ulceration superimposed on florid changes of chronic cholecystitis. No stones were recovered from the biliary tree or gallbladder. Acute or chronic cholecystitis was reported on histological examination. He made a good recovery and remains well over 2 years later.

A consultant hepatobiliary surgeon and two consultant radiologists were asked to report on these films as part of a retrospective study of ninety PTC films. They were not aware of the final diagnosis. All three agreed that the patients had a dilated biliary tree and the delayed movement of contrast into the duodenum suggested the presence of obstruction in the periampullary region. In the first patient the obstruction was reported as neoplastic with a probability of 95–100 per cent, while in the second patient a neoplastic cause was thought likely (probability 60, 70 and 100 per cent).

Discussion

The great majority of duodenal diverticula are asymptomatic incidental findings even in jaundiced patients. However, they are reported as causing obstructive jaundice due to anatomical distortion of the common bile duct, diverticulitis or enterolith formation[1–4]. Our two case reports illustrate that cholangiographic appearances mimicking periampullary tumour can be associated with such diverticula and highlight the need for endoscopic biopsy in all patients thought radiologically to have periampullary lesions. Before such diverticula can be considered as a cause of biliary obstruction we suggest that the following criteria should be fulfilled: the presence of the diverticulum should be confirmed endoscopically or radiologically; the patient should have had at least one episode of obstructive jaundice documented clinically, biochemically and radiologically; and no other causes of obstruction should be demonstrated. It is particularly important to exclude the presence of gallstones and an arbitrary follow-up period of, say, 2 years might be used to exclude occult neoplasia of the periampullary area.

The exact cause for obstructive jaundice in our patients remains speculative, but both required laparotomy because of gallbladder inflammation and although no gallstones were recovered it is conceivable that earlier passage of calculi through the papilla of Vater could cause inflammation and obstruction. Leese *et al.*[5] have recently emphasized the clinical and biochemical similarities between patients with non-neoplastic periampullary 'pseudotumour' and those with periampullary neoplasms. Like these authors, we would recommend avoidance of laparotomy if at all possible when endoscopic biopsy does not confirm neoplasia in patients with periampullary obstruction. The recent availability of endoscopic sphincterotomy may now allow the jaundice to subside and permit inflammation to resolve. If such patients do come to laparotomy, radical surgery must not be undertaken unless open biopsy and frozen section examination confirms the presence of cancer.

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Short note

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Gastrostomy-induced duodenal obstruction after gastric bypass

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We present our experience of gastrostomy in 500 morbidly obese patients who underwent Roux-en-Y gastric bypass, emphasizing its complications and relating them to those described in the surgical literature[1].

Patients and methods

A total of 500 gastrostomies were routinely constructed in the distal gastric pouch of morbidly obese patients who underwent a Roux-en-Y gastric bypass[2]. A large Foley catheter was inserted into the distal stomach via the anterior antral wall and secured with a purse-string suture. The stomach was anchored to the abdominal wall and the tube brought out through a stab wound. If the approximation of the stomach to the abdominal wall was difficult, the tube was brought out through the midline incision. The tube was secured to the skin and the balloon inflated with saline. The gastrostomy tube was left open for 4 days. It was removed 3–6 months postoperatively, when the patient tolerated normal intake of soft food.

Case reports

Case 1

A 22-year-old morbidly obese woman (141 kg) underwent a Roux-en-Y gastric bypass[2] with a distal gastrostomy brought out through a stab wound. On the sixth postoperative day, coffee-ground secretion was noticed around the gastrostomy tube, while clear bile drained through the tube itself. She complained of right abdominal pain and was pyrexic (39°C). Gastrografin® swallow under fluoroscopy disclosed no evidence of an anastomotic leak. Gastrografin injected through the gastrostomy revealed the tip of the catheter in the duodenum with its inflated balloon obstructing the gastric outlet. The distal gastric pouch was extremely distended. The balloon was deflated and the tube withdrawn into the stomach. However, high fever persisted and necrotizing fasciitis of the abdominal wall developed from which she died on the twenty-second postoperative day.

Case 2

A 28-year-old 119 kg woman was treated with a Roux-en-Y gastric bypass. The gastrostomy was brought out through the operative incision. On the sixth postoperative day coffee-ground material appeared around the gastrostomy tube with secondary wound infection. Gastrografin injected through the tube revealed obstruction of the duodenum by the tube's balloon. Pulling the tube back into the stomach resolved the problem. The patient was discharged on the thirteenth postoperative day.

Discussion

Our experience with tube gastrostomy, in a unique group of morbidly obese patients who underwent gastric bypass, is presented.

Reported clinical studies show that gastric outlet obstruction is a frequent complication of tube gastrostomy. Its manifestations are epigastric discomfort and vomiting[3–6]. Of 500 gastrostomies which we have performed during Roux-en-Y gastric bypass, 10 had leakage of clear or white-stained material about the tube. It usually appeared on the fifth day, was self-limited and no special measures were needed for its management. Two patients complained of epigastric pain with concomitant coffee-ground leakage around the tube. This leakage reflected the gastric outlet obstruction and dilatation induced by migration of the tube's balloon into the duodenum. Vomiting, a characteristic of gastric outlet obstruction, is prohibited by the two rows of staples separating the stomach proximally and is not an immediate sequel. The distal stomach dilates gradually and produces the coffee-ground material, which is evacuated through the track around the tube.

Gastrostomy-induced duodenal obstruction has been accepted as a minor complication, usually appearing months or years after surgery[3,5]. To the best of our knowledge, duodenal obstruction after gastric bypass with this unique presentation of epigastric pain, absence of vomiting, leakage of coffee-ground material around the gastrostomy, early occurrence after surgery and potential lethality, has not been reported. Nevertheless, we think that construction of tube gastrostomy during gastric bypass is generally a safe procedure. In this series, gastric outlet obstruction was a rare complication (0·4 per cent) which should easily be managed with astute diagnosis. A high index of suspicion, radiological confirmation and prompt reposition of the tube may obviate subsequent potentially lethal events.

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Intestinal Kaposi's without AIDS

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Kaposi's sarcoma (KS) was first described by Moritz Kaposi in 1872 (reference 1) and is endemic in Africa, comprising up to 10 per cent of all malignancies[1]. Sporadic cases have occurred in Europe affecting elderly men and involving primarily skin and mucous membranes. Since 1981, an epidemic form of KS in association with the acquired immunodeficiency syndrome (AIDS) has assumed increasing importance. We describe a case in a 22-year-old white British man presenting with abdominal symptoms and signs.

Case report

A 22-year-old heterosexual married man presented with an 8-week history of colicky central abdominal pain and weight loss associated with occasional vomiting and bloody diarrhoea. A barium follow-through revealed an ileocolic intussusception (*Figure 1*, above).

At laparotomy the ileocolic intussusception was confirmed, together with slightly enlarged regional nodes. Upon reduction a 3-cm polypoid caecal tumour was found as the apex of the intussuscipiens, for which a right hemicolectomy was performed.

The patient made an uneventful postoperative recovery and when last seen 11 months postoperatively was well with no signs of recurrence.

The histology showed a widespread tumour composed of interweaving bands of pleomorphic spindle cells and poorly formed vascular structures (*Figure 1*, below). Foci of tumour were present in the subserosa and in many regional nodes. This tumour was multifocal in origin with an unusual pattern. After discussion with Professor Tighe at St. Thomas' Hospital, a firm diagnosis of Kaposi's sarcoma was made. As a result of this diagnosis, repeated HIV tests were carried out on the patient and his wife both locally and at St. Stephen's Hospital. No evidence of AIDS was found. Blocks of tumour tissue were sent to the Institute of Dermatology for factor VIII and Ulex staining, both supporting a diagnosis of Kaposi's sarcoma. The more specific endothelial cell monoclonal marker stains, EN4 and PAL E, could not be done as they require specially fixed tissue which was not available. Dr Neil Smith at the Institute reviewed the histology knowing the patient showed no evidence of AIDS. He confirmed that the findings were consistent with the diagnosis of Kaposi's sarcoma.

Discussion

Although Kaposi's first description was of 'multiple pigmented sarcoma of the skin'[1], gastrointestinal involvement occurs in 10 per cent of cases[2] and in 50 per cent of those associated with HIV virus[3]. Gastrointestinal KS is usually clinically silent although haemorrhage, perforation[4], obstruction[5] and protein-losing enteropathy have occurred. Only one previous case of intussusception due to KS has been reported, this being in a 38-year-old African man[5].

We believe that this is the first recorded European case of intussusception attributable to KS. In view of the increasing publicity over AIDS it is worth remembering that not all young patients with Kaposi's sarcoma necessarily have AIDS.

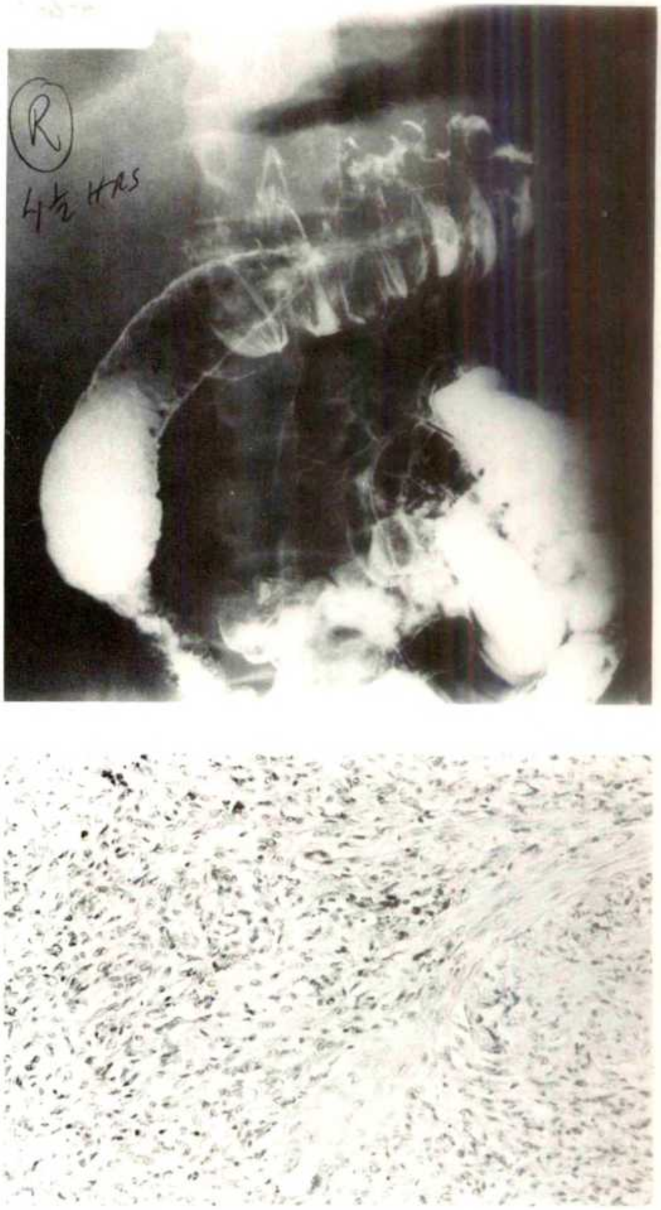

Figure 1 *The X-ray (above) and microscopy (below) results from a patient with Kaposi's sarcoma*

Acknowledgements

We are grateful to Mr A. W. R. Williamson, Consultant Surgeon, Kent and Sussex Hospital for permission to report this case. We would also like to thank Professor J. R. Tighe of St. Thomas' Hospital and Dr Neil Smith of the Institute of Dermatology for their help with the histology.

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Gluteal artery aneurysms

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Two cases of gluteal artery aneurysm following penetrating trauma to the buttock are presented. Both cases were misdiagnosed as abscesses and were incised in the casualty area, resulting in massive haemorrhage. The surgical exposure for this pathology is discussed.

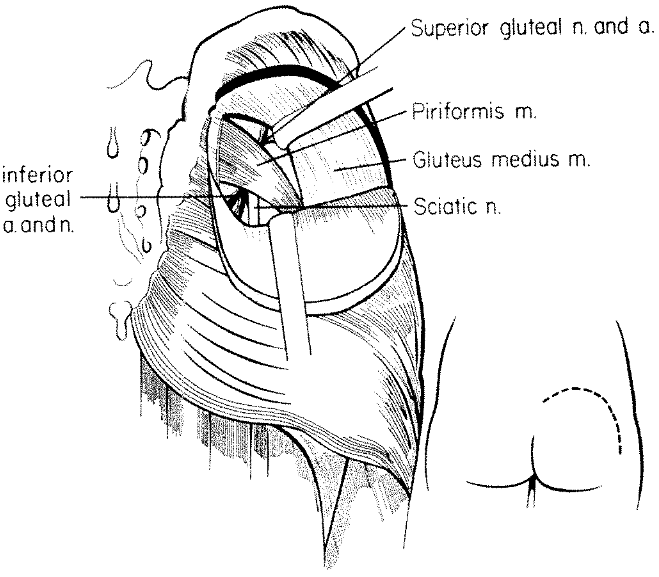

Figure 1 *Incision and operative exposure for gluteal arteries: n, nerve; a, artery; m, muscle*

Case reports

Case 1

A 35-year-old man was seen in the casualty department 2 weeks after being stabbed in the right buttock. The buttock was swollen, inflamed, and painful. The diagnosis of an infected haematoma was made and an incision was performed over the pointing area. Torrential arterial bleeding followed and the systolic blood pressure dropped to 60 mmHg within minutes. The bleeding was partly controlled by direct compression over the wound and the patient was taken to the operating theatre. A ruptured false aneurysm arising from the main trunk of the superior gluteal artery was found. Suture ligation of the feeding vessel was performed from inside the aneurysm. The patient was transfused intra-operatively with 6 units of blood. The postoperative recovery was uneventful.

Case 2

A 22-year-old man was seen 3 weeks after a penetrating injury of the right buttock. The affected area was swollen, inflamed and painful. The lesion was thought to be an abscess and it was incised under local anaesthesia. Massive arterial bleeding followed and the blood pressure became unrecordable within minutes. Attempts to control the bleeding by direct compression over the buttock were unsuccessful. The wound was then extended and the cavity was tightly packed with a large swab. This manoeuvre was successful and the patient was taken to theatre where a ruptured aneurysm of the superior gluteal artery was found and the vessel was sutured–ligated. The patient was transfused with 5 units of blood intra-operatively. The postoperative recovery was uneventful.

Discussion

The superior gluteal artery is a large vessel originating from the posterior division of the internal iliac artery. It leaves the pelvis through the greater sciatic foramen and it emerges above the piriformis muscle. The inferior gluteal artery is found at the lower border of the piriformis. The well-protected position of these vessels makes post-traumatic gluteal artery aneurysms very rare: less than ten cases have been reported in the English literature in the past 10 years. The most common causes are pelvic fractures and penetrating injuries to the buttock, in that order. Penetrating injuries usually involve the superior gluteal artery, and fractures of the pelvis, the inferior gluteal artery[1].

The false aneurysm may present within a few weeks of or many months after the initial injury[1,2]. The typical presentation is a painful swelling of the buttock with or without a bruit or signs of inflammation. Occasionally, compression of the sciatic nerve by an expanding aneurysm or haematoma may occur[2]. Because of the rarity of this aneurysm and the signs of inflammation which are often present the diagnosis of an abscess may be made with dramatic consequences. Auscultation for a bruit in all buttock swellings following trauma is of paramount importance. An angiogram will make the definitive diagnosis.

The importance of adequate exposure for the management of these lesions cannot be overemphasized. Attempts to control the bleeding through a transverse incision in the buttock and splitting of the gluteus maximus muscle are usually futile and massive exsanguination may occur, especially when the lesion is deep to the sciatic foramen. Furthermore, there is a risk of accidental injury of the sciatic nerve[3].

It is recommended that the patient be put in the prone position and a cushion placed under the pelvis on the side of the lesion. The abdomen should always be prepared and draped. The incision of choice should start at the greater trochanter, curve upwards parallel to the iliac crest and end at the posterior superior iliac spine (*Figure 1*). The gluteus maximus is divided as close as possible to the iliac crest where the muscle is aponeurotic[3]. This musculocutaneous flap is elevated and the underlying structures are now accessible. Upward traction of the gluteus medius will expose the main trunk of the superior gluteal artery, at the upper border of the piriformis. The inferior gluteal artery is readily accessible at the inferior border of the muscle (*Figure 1*). Suture–ligation of the vessel which feeds the aneurysm is then performed.

If the lesion involves the vessel before its emergence from the sciatic foramen, control of the bleeding is extremely difficult. In these cases proximal control is gained through an oblique abdominal incision and extraperitoneal isolation of the internal iliac artery. Some authors advocate retroperitoneal proximal control before they proceed to perform the buttock incision[2]. Ligation of the internal iliac artery from inside without directly suturing the bleeding point is not recommended because of the rich collateral network between the internal and external iliac systems.

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Choledochocele: treatment by endoscopic sphincterotomy

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A choledochocele is a cystic dilatation of the intraduodenal portion of the common bile duct with herniation into the duodenal lumen[1]. This rare abnormality may present clinically as episodic right upper abdominal pain accompanied by nausea and vomiting, intermittent biliary colic with abnormal liver function tests, and recurrent pancreatitis[2].

We report a patient with a long history of intermittent colicky abdominal pain in whom a choledochocele was found by endoscopic retrograde cholangiography and who was treated successfully by endoscopic sphincterotomy.

Case report

A 37-year-old woman was admitted to our hospital in January 1985 because of attacks of upper abdominal colicky pain since 1970. The attacks occurred 2–3 times a week and usually lasted for some hours. The pain always radiated to the back, and was sometimes accompanied by slightly abnormal serum alkaline phosphatase and aspartate aminotransferase levels. In 1971 a cholecystectomy was performed but did not influence the pain. Intravenous cholangiography was normal.

Physical examination on admission revealed no pathological findings. Ultrasonography of the biliary ductal system and the pancreas demonstrated no abnormalities. However duodenoscopy with a side-viewing instrument showed, at the site of the papilla of Vater, a hemispherical smooth mass protruding into the duodenal lumen. The papillary orifice was identified at the underside of the tumour (*Figure 1*). The orifice was cannulated and contrast medium was instilled into the biliary system. The hepatic ducts and the intrahepatic biliary system were not dilated. The common bile duct was slightly dilated, compatible with the previous cholecystectomy, and its distal part terminated in a cystic structure projecting into the duodenal lumen (*Figure 2*). Subsequently a papillotome was inserted into the orifice and an incision was made up to the site where the upper side of the cyst disappeared into the duodenal wall. There were no complications. During a follow-up of more than 2 years the patient has remained completely free of attacks of pain.

Discussion

Cystic dilatations of the biliary tract have been classified by Alonso-Lej *et al.*[3] into three types: type I, cystic dilatation of the common bile duct; type II, common bile duct diverticulum; and type III, choledochocele. This classification has been expanded by Todani *et al.*[4] who added three types: type IV A, multiple intrahepatic and extrahepatic cysts; type IV B, multiple extrahepatic cysts; and type V, cystic dilatation of the intrahepatic ducts (Caroli's disease). The choledochocele is one of the rarest types and occurs in 1·4–5 per cent of reported cases of bile duct cysts[2].

The pathogenesis of the choledochocele remains an enigma. In some patients both sides of the cyst wall are lined by duodenal mucosa which suggests that the choledochocele may represent a congenital duodenal duplication[5–7]. In other patients the inside of the cyst is lined by biliary mucosa which suggests that it may represent a true diverticular enlargement of the common bile duct[1,8,9]. This enlargement may be due to congenital local weakness of the wall of the common bile duct, to congenital or acquired obstruction of the sphincter of Oddi, or to neuromuscular dysfunction of the sphincter. In the latter two circumstances chronic reflux of pancreatic juice into the biliary tree may play an additional role in formation of the cyst[1,10,11].

As opposed to patients with other types of common bile duct dilatations most patients with a choledochocele are older than 20 years when symptoms start[12]. It is usually a long time before the correct diagnosis is made and the duration of symptoms may vary from some months to more than 20 years[1,5]. In many patients recurrent abdominal pain, which is often accompanied by nausea and vomiting, is the major complaint[1,5,7]. The pain probably occurs when the choledochocele is distended and acts as an obstructing lesion in the duodenum[5,8,13]. Gallstones develop in the choledochocele in about 30 per cent of the patients and may cause complications such as recurrent pancreatitis, obstructive jaundice or cholangitis[1,9,10,14,15]. However, pancreatitis and cholestasis may also occur in patients without stones, the first probably due to reflux of bile into the pancreatic duct with subsequent activation of pancreatic enzymes and the second as a consequence of distension of the cyst causing impaired biliary drainage[6,11,13,16,17].

Additional anomalies of the biliary tract (double bile duct, double, absent or multiseptate gallbladder, accessory hepatic ducts, bile duct atresia and bile duct stricture) and also anomalies of the urinary tract (hypoplasia or agenesis of the kidneys, polycystic kidney disease, medullary sponge kidneys and megalo-ureter) are frequently associated with other types of bile duct cysts[2,12,18,19]. The findings in our patient suggest that congenital anomalies of the urinary tract too are associated with a choledochocele.

A choledochocele is not easy to diagnose. As in our patient, the cyst may be overlooked at intravenous cholangiography or ultrasonography[1,9–11,20]. At an upper gastrointestinal series it may sometimes be seen as a filling defect in the contrast medium at the medial side of the second part of the duodenum[1,5–7,9]. At duodenoscopy it is seen as a smooth, round, periampullary tumour[8,11,21]. The diagnosis is established with certainty by percutaneous transhepatic or endoscopic retrograde cholangiography[8,10,11,13,16].

In the past a choledochocoele was usually treated by choledochoceleduodenostomy, choledochoduodenostomy, sphincteroplasty or surgical excision[10,14,16,17]. Recently a number of patients have been treated endoscopically, either by endoscopic removal of the cyst by a diathermy loop or by endoscopic sphincterotomy[8,11,21]. We also performed an

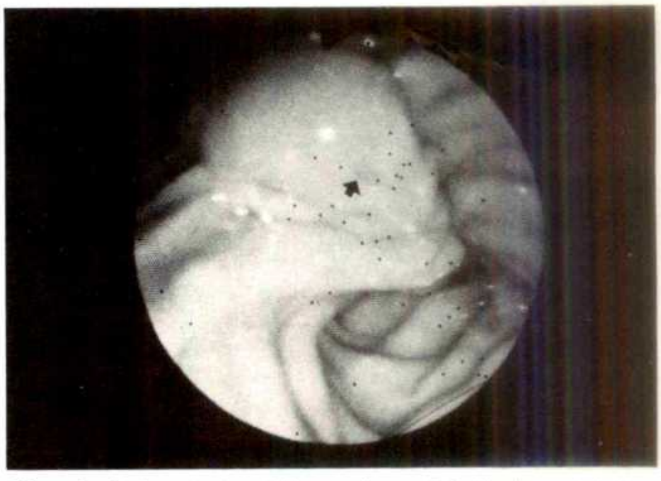

Figure 1 *Endoscopic view of the second part of the duodenum depicting a choledochocele. The orifice is seen at the underside of the cyst (arrow)*

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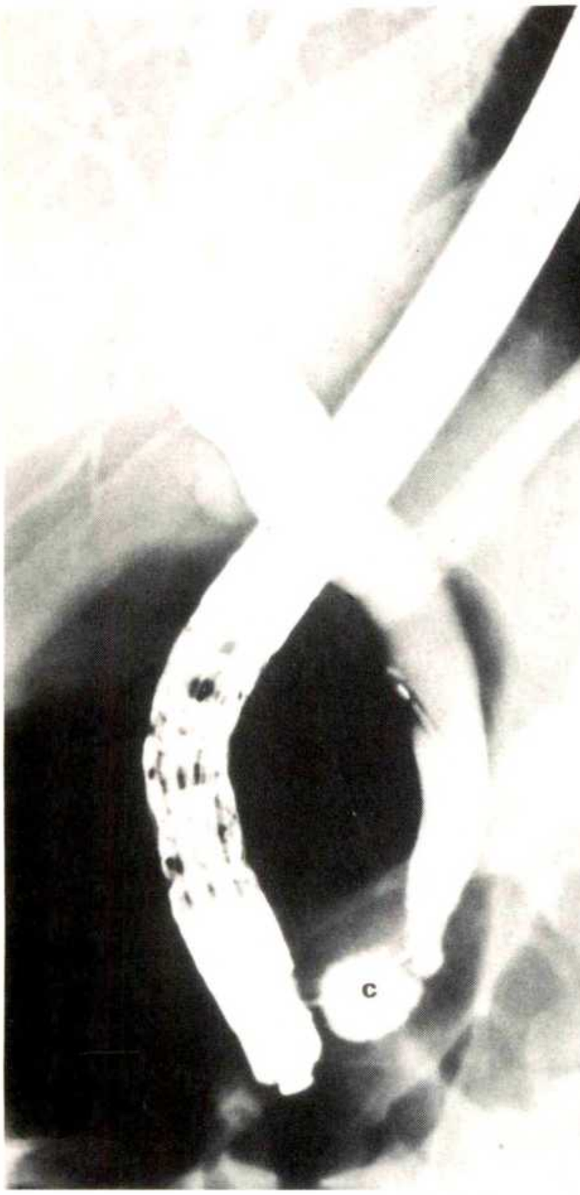

Figure 2 *Endoscopic retrograde cholangiogram showing (c) the choledochocele*

endoscopic sphincterotomy in our patient and afterwards she was free of symptoms. It has been demonstrated that bile duct carcinomas occur in up to 28 per cent of patients with type I and II cysts even after internal drainage and therefore complete excision of these cysts, if possible, is generally advocated[15,22–24]. However until now only one case of carcinoma developing in a type III cyst has been reported[12] and thus sphincterotomy seems to be an acceptable mode of treatment for a choledochocoele, the more so as the remnants of the cyst may be surveyed easily by endoscopy.

In conclusion, a choledochocele should be considered as a possible cause in patients with unexplained recurrent upper abdominal colicky pain, urinary tract anomalies may be associated with this type of bile duct cyst, and it can be treated successfully by endoscopic sphincterotomy.

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Correspondence

Complete rectal prolapse

Sir

I would like to congratulate Mann and Hoffman (*Br J Surg* 1988; 75. 34–7) on their excellent paper and would agree that abdominal rectopexy should continue to form the basis of surgical treatment and that lesser procedures which are advocated on grounds of safety are not justified, except in the most extreme circumstances. Nevertheless, there are simpler forms of abdominal rectopexy which also give good results[1]. Mann and Hoffman had no mortality in their series and this is a considerable achievement. Nevertheless they did have a considerable number of postoperative complications and a long hospital stay of 19 days. This is only to be expected when using quite a complicated operation in an elderly population. Less mobilization of the rectum with the insertion of four sutures posteriorly between the sacral fascia and the posterior wall of the rectum has, in our experience, proved sufficient to prevent any recurrence with much lower morbidity and no mortality.

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1. Graham W, Clegg JF, Taylor TV Complete rectal prolapse repaired by a simple technique. *Ann R Coll Surg Engl* 1984 **66**. 87–9.

Loose arterial sutures

Sir

We read with interest the paper by Blackett and Heard (*Br J Surg* 1988; 75: 112) describing their technique of tightening loose arterial sutures. We have found that an ordinary suture tie at the base of the loop of a monofilamentous material such as Prolene® is prone to slip easily and thus the right tension at the anastomosis is lost.

We therefore recommend our technique which has proved useful in arterial as well as other anastomoses for the past 10 years We have used a skin hook instead of a nerve hook as recommended by the authors A Ligaclip (Ethicon Ltd., UK) placed at the base of the loop would ensure that the correct tension is preserved.

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Pre-operative parathyroid localization

Sir

The recent article on pre-operative parathyroid localization is a timely review of the methods and difficulties involved in the search for parathyroid tumours (*Br J Surg* 1988, 75: 97–8) However, no mention was made of the equally important intra-operative localization method and, in particular, Methylene Blue. This method has proved to be reliable and reproducible in over 150 patients to date[1]. It has been particularly useful in tumours of the mediastinal, intrathyroid glands and where more than five glands exist. In comparison with other methods, it is cost-effective as the materials required are relatively cheap and readily available in all hospitals

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Laser induced intravascular coagulation for the treatment of acute peptic ulcer bleeding

Sir

We read with interest the article by Rogers *et al* (*Br J Surg* 1988, 75. 16–17) which suggested that treatment of bleeding gastric ulceration by oversewing the lesion is effective. They conclude that because of the development of effective anti-ulcer drugs over the last decade there is no longer a need to perform an ulcer healing procedure when operating to control haemorrhage They draw attention to the increasing number of elderly patients with concomitant medical conditions requiring surgery and emphasize the need to reduce surgical trauma

We would like to present an experimental non-surgical approach to control haemorrhage from peptic ulcers that would minimize trauma to the patient. The technique employs the concept of laser-induced intravascular coagulation. This is achieved with a new type of laser—the Holmium laser. It has a wavelength of 2·1 μm which falls between the Nd.YAG (1·06) and the CO_2 (10·6) laser which both have established clinical applications. Theoretically one might expect the Holmium laser to be a better photocoagulator than the CO_2 laser and a better 'light knife' than the Nd.YAG. In addition, the ability to transmit the beam through an optical fibre may render this laser valuable for various endoscopic procedures.

During our experiments on dogs, we were impressed with its ability to perform coagulation at a precise location in a blood vessel even within the blood stream This led us to embark on a project designed to test the ability to seal blood vessels without resorting to surgery. In order to create a model of acute peptic ulcer bleeding in anaesthetized dogs, the gastroduodenal artery was severed at the posterior wall of the duodenum under direct vision through a gastrotomy. A catheter was introduced via the femoral artery and guided under X-ray control into the coeliac trunk and selectively into the gastroduodenal artery to a point 1 cm proximal to the bleeding site. The laser optical fibre was inserted into the artery through the catheter. The artery was successfully occluded in a consecutive series of five dogs using a laser pulse of 2 W, thus achieving haemostasis Perforation of the vessel did not occur because the catheter maintained the optical fibre in the centre of the arterial lumen.

The results of these preliminary experiments are encouraging. Laser induced intravascular coagulation may find clinical application as an alternative to open surgery to control acute peptic ulcer haemorrhage.

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Vascular trauma

Sir

It is perhaps worth adding a note on the use of a temporary arterial shunt after the review of vascular trauma by Blacklay *et al* (*Br J Surg* 1987; 74 1077–83).

As the authors stated, immediate repair of a damaged artery restores distal limb perfusion as quickly as possible. However, if an adjacent fracture has to be manipulated, the vascular repair may be disturbed. This sequence can be anticipated in a combined popliteal artery injury and an unstable tibial plateau fracture. Insertion of a Javid or similar shunt to reperfuse the lower leg will minimize ischaemic damage whilst the fracture is stabilized. The arterial repair is then undertaken and the shunt removed.

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Lymphangiosarcoma

Sir

We were interested to read the report of Gajraj *et al.* (*Br J Surg* 1987, 74: 1180) concerning their unfortunate patient with locally advanced lymphangiosarcoma Two points arise from their case report.

Firstly, the histological diagnosis of angiosarcoma is complicated by variable terminology and the lack of a standard nomenclature[1]. Lymphangiosarcoma is the name given to angiosarcoma developing in a lymphoedematous limb, but it does not necessarily imply that the tumour arises from lymphatic endothelium Histologically, lymphangiosarcoma is identical to other angiosarcomas[1–4] The only histological feature which may be unique to lymphangiosarcoma is the presence of lymphangiomatosis[5]. The prognosis for angiosarcoma is generally poor[1,2].

Secondly, angiosarcoma is characterized by frequent local recurrences after wide excision and the occasional long-term survivor after radical amputation[1,2,6]. This suggests that the disease is regionally confined 'early' in its natural history. We would agree that evidence from the literature supports early, radical surgery for this disease and that other methods have usually been disappointing[1,6,7]

Sordillo *et al* [7] have described one patient who had a complete response to regional chemotherapy with intra-arterial cyclophosphamide The series of Krementz *et al.*[8] showed that the response rate of sarcomas in general is much greater after regional perfusion than after systemic administration of cytotoxic drugs We have treated two patients with recurrent angiosarcoma by isolated limb perfusion with high dose melphalan. One had refused further amputation and the other had a palliative perfusion for advanced disease. In each case there has been an encouraging response to perfusion and we suggest that this treatment should be considered in the management of appropriate cases of angiosarcoma.

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Radionuclide ejection fraction

Sir

Morecroft and Thomas emphasize (*Br J Surg* 1988; **75**. 188) that a normal left ventricular ejection fraction (LVEF), determined by radionuclide angiography, is not a guarantee against the presence of severe myocardial ischaemia or resulting perioperative death in patients undergoing abdominal aortic surgery They also suggest that the test is of value in identifying those patients with poor left ventricular function who require close perioperative monitoring

Routine use of the test in all patients being assessed for abdominal aortic surgery has identified several in whom the history, clinical examination and ECG had indicated a low cardiac risk, whereas the LVEF had been very poor (15 per cent in a recent case) Thus, I believe it is important to carry out the test in all patients, rather than only those thought to be at particular risk.

Regarding use of the LVEF to determine the level of perioperative monitoring, the study by Joyce *et al.*[1] may be pertinent These workers found, in a small study, that Swan–Ganz catheter monitoring appeared not to be of value when the LVEF was > 50 per cent. My regimen entails use of a Swan–Ganz catheter when the LVEF is < 40 per cent. When the LVEF is < 35 per cent the patient is admitted to the intensive treatment unit the day before surgery for insertion of a Swan–Ganz catheter, and blood volume is expanded to the optimal left ventricular filling pressure.

Of the 92 patients who have undergone elective abdominal aortic surgery employing the above regimen, 2 died within 30 days of operation. One of these patients, who had a normal LVEF, died suddenly soon after operation, and post-mortem examination showed evidence of myocardial infarction.

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1. Joyce WP, Ameli FM, Provan JL, McEwan MP, Jelewich S, Jones DP. Do all patients undergoing abdominal aortic surgery require central haemodynamic monitoring? *Br J Surg* 1988, **75** (Abstract) 393

Testicular torsion after orchidopexy

Sir

We have read the case reports by Steinbruchel and Hansen (*Br J Surg* 1988; 75: 47) with great interest. In this connection we wish to report a patient who presented with torsion of the testis on the side opposite to that of a previous orchidopexy The patient, aged 39 years, presented with signs and symptoms suggestive of torsion of the left testis The testis was explored and the diagnosis confirmed After untwisting, it was placed in the dartos pouch Nearly 20 years before this presentation he had had a right orchidopexy performed because of undescended testis on that side. Unfortunately, any anatomical abnormality, if present; in the right testis had not been documented

Because of the above case, we feel that during an orchidopexy for undescended testis, it is important to look carefully for any abnormalities such as high investment of tunica or separation of the epididymis from testis by a mesentery If such anomalies, which will make the testis prone to torsion and likely to be bilateral, are noted then the opposite testis should be explored even if it is normally descended and placed in the dartos pouch We do appreciate that it becomes difficult to recognize high investment of tunica in a canalicular testis particularly if there is an associated complete hernial or hydrocele sac. Then the important anatomical consideration would be strong attachment of tunica to the posterolateral aspect of testis and epididymis. If such attachments are lacking, the tunica completely surrounds the testis and epididymis, producing a 'bell-clapper' anomaly[1].

The goal in preventing testicular torsion is to create adhesions between tunica albuginea and scrotal wall Morse and Hollabaugh[2] demonstrated in experimental animals that best adherence is achieved by allowing broad contact between tunica albuginea and the scrotal wall and extended this finding to clinical practice by creating a window in the tunica (window orchidopexy) If this line of reasoning is correct, then much broader contact can be obtained by incising the tunica, everting it backwards and placing the testis in the subcutaneous dartos pouch[3]. This technique, which is commonly employed in the management of undescended testis, is a simpler procedure than attempting to create a window in the tunica. Perhaps there is a case for controlled studies in laboratory animals to ascertain which of the techniques induces more permanent adhesions

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1 Sheldon CA. Undescended testis and testicular torsion. *Surg Clin North Am* 1985; **65**. 1303–29.
2. Morse TS, Hollabaugh RS The 'Window' orchidopexy for prevention of testicular torsion *J Pediatr Surg* 1977, **12**. 237–40.
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Subclavian vascular injuries

Sir

With reference to the article on subclavian vascular injuries by Mr Demetriades and colleagues (*Br J Surg* 1987; **74**. 1001–3), we have observed that mere release of soft tissues from the medial one-third of the clavicle may control subclavian venous bleeding without the need for direct vascular control

We were faced with the problem of subclavian venous bleeding during the course of dissection of a mass of caseating tuberculous lymph nodes in the right supraclavicular fossa of a 25-year-old woman. The bleed was controlled by packing, only to recur when the pack was removed, and matters were aggravated by the deep Trendelenburg position she had to be given in order to minimize the risk of air embolism. The bleeding was seen to come from a rent in the postero-inferior aspect of the right subclavian vein close to its junction with the internal jugular. We divided the clavicle at the junction of its middle and medial thirds and mobilized the medial end subperiosteally up to the sternoclavicular joint to facilitate exposure of the vessel. To our surprise (and relief), this was followed by immediate cessation of bleeding No vascular suture was required although an 'insurance' surgical packing was employed. She did not bleed thereafter

Later, on reviewing the relevant anatomy[1], it appeared that mobilizing the clavicle had freed the clavipectoral fascia in this region where it splits to enclose the subclavius muscle in the inferior groove on the bone. The clavipectoral fascia blends with the sheath surrounding the subclavian vessels (this sheath continues as the axillary sheath). The clavicle is convex anteriorly along its medial two-thirds and, through the clavipectoral fascia, probably tends to 'tent' the subclavian vein and therefore keep a tear therein open. Freeing the fascia from the clavicle collapses the former and helps to close a venous tear.

Tuberculous neck nodes can be notoriously difficult to remove as adherence to the great veins is common. These nodes often continue as a chain into the mediastinum and, in his enthusiasm for chasing the elusive low-set gland, the surgeon may either cut a vein or tear it while pulling on a node.

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1. Williams PL, Warwick R, eds *Gray's Anatomy* 36th ed. Edinburgh· Churchill Livingstone. 1980.

Author's reply

Sir

The observation made by Drs Bhargava and Narayanan is an interesting one. However I think that a torn subclavian vein should always be managed definitively, by means of repair or ligation. If the exposure is difficult, as in proximal injuries, a median sternotomy may be necessary Release of the soft tissues from the medial part of the clavicle, as suggested by the authors, may achieve temporary control of the bleeding, but I feel that this should always be followed by a definitive procedure. Catastrophic bleeding may occur when the patient wakes up, coughes or sneezes.

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Approach to ingrowing toenails

Sir

The recent article by M.M. Issa and W.A Tanner (*Br J Surg* 1988, **75**· 181–3) suggests that segmental ablation of nail bed by the 'new' combination of surgery and chemical ablation can give good results in the treatment of ingrowing toenails Unfortunately, however, they appear to have reviewed only the medical literature on the subject and neglected the chiropodial literature and this has led them to state that the combination therapy has not previously been tried. The first report of this treatment was probably by Boll[1] in 1945, although the description of his procedure is admittedly a little vague In 1962, however, Suppan and Ritchlin[2] clearly describe this combination therapy reporting 3 recurrences from 240 operations.

I was also disappointed to see the results of a comparative trial of nail ablation reported at 6 months Recurrences can and do occur later than this after nail ablative procedures. Townsend[3] reports recurrences after more than a year and in our own study one of seven recurrences after surgical ablation and two of six recurrences after phenol ablation appeared in the period 12–36 months postoperatively.

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Inguinal hernia

Letter 1

Sir

Mr Marsden in his detailed analysis of a personal series of operations for recurrent hernia (*Br J Surg* 1988; **75**: 263–6) makes several statements, which prompt me to write in response.

He considers that use of a mesh would probably have improved his results of operations for recurrent hernia, and with this I agree, but I would go further: for the past 20 years I have used synthetic mesh for the primary repair of inguinal hernia, first via the preperitoneal route[1] and then, since 1980, via a standard anterior approach through the inguinal canal. Complications of wound sinuses and extrusion, hitherto associated with the use of prostheses, have not been encountered, presumably because of the improved tissue compatibility of currently available materials.

The advantage of using synthetic mesh for the initial operation for inguinal hernia is that the whole of the posterior wall of the inguinal canal including the internal inguinal ring is reconstructed and rendered competent instantly; as the tissues are not sutured under tension (as they tend to be when Bassini operations are carried out) patients are notably more comfortable postoperatively, and are without incidence of iatrogenic femoral hernia which Mr Marsden encountered in some of his cases.

If, as I do, one believes that the basic pathology of acquired inguinal hernia is failure by degeneration of the fascia transversalis where it forms the posterior wall of the inguinal canal and the internal inguinal ring, then reconstruction of the fascia transversalis in the canal must be the logical and essential element in any repair; this objective is achieved by the strategic insertion of synthetic mesh.

That the best solution to the problem of recurrent inguinal hernia is prevention, by improved techniques of primary repair, cannot be denied, the question is what repair; on the basis of experience, I submit that primary synthetic mesh hernioplasty must be a strong contender.

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Letter 2

Sir

I should like to support Mr Marsden (*Br J Surg* 1988; 75: 263–6) in favouring complete closure of the canal when dealing with recurrent inguinal hernias. However, my early experience with cord section included two patients who developed testicular necrosis, and even elderly men may be reluctant to undergo orchidectomy. For nearly 20 years I have replaced the testis in the abdomen followed by complete canal closure in difficult or recurrent hernia repairs[1]. Patients have accepted it without demur In elderly and unfit patients the slight theoretical risks of intra-abdominal placement of the testis can be ignored.

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1. Kirk RM. Intra-abdominal replacement of the testis as an aid to the repair of difficult and recurrent inguinal hernias *Br J Surg* 1974; **61**· 538.

Arterial disease

Sir

The leading article by Messrs Campbell and Wolfe (*Br J Surg* 1987, **74** 1075–6) appears to perpetuate the motion that a pre-operative arteriogram is essential for the planning of all vascular reconstructive procedures, with the possible exception of carotid endarterectomy (and presumably aortic aneurysm repair). However there is now a wealth of evidence to indicate that in critically ischaemic limbs patent arteries in the calf and foot may fail to opacify by this means and that reliance on pre-operative arteriograms can lead to unnecessary amputations[1]

The use of optical magnification, the extended utilization of autogenous vein offered by the *in situ* long saphenous vein technique and the use of arm veins permits bypass to whatever distal vessels appear patent on Doppler insonation. Consequently operative strategy can be decided on the basis of clinical signs and Doppler insonation alone[2] The fear that omission of routine pre-operative arteriography might deny these patients the option of treatment by transluminal angioplasty has not been validated by personal experience in over 160 cases; intra-operative prebypass arteriography after selection for distal bypass by non-invasive testing has invariably revealed long femoropopliteal occlusions and multisegment infrapopliteal disease, unsuitable for percutaneous dilatation.

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1 Ricco JB, Pearce WH, Yao JST *et al* The use of operative prebypass arteriography and Doppler ultrasound recordings to select patients for extended femoro-distal bypass. *Ann Surg* 1983; **198**: 646–53.

2 Shearman CP, Gwynn BR, Curran F *et al.* Non-invasive femoropopliteal assessment. is that angiogram really necessary? *Br Med J* 1986, **293**· 1086–9.

Authors' reply

Sir

While agreeing with some of Mr Simms' points we feel that he has misinterpreted our message. We did not suggest that a poor arteriogram should lead to amputation, and have previously published on the value of Doppler insonation[1]

We entirely agree that femorocrural bypass should now be common-place but we find that a transfemoral puncture into a strong femoral pulsation and a concentration on the distal vessels alone leads to good opacification of the segments of vessel patent in the lower calf. This policy has resulted in a primary amputation rate of less than 8 per cent for critical ischaemia. On-table perfemoral arteriography may achieve the same purpose but in our experience the quality is better in the radiology department. We only explore the popliteal artery if we intend to revascularize this vessel.

We also use Doppler insonation of ankle vessels but only as an adjunct to arteriography. Since segments of more than one vessel may be patent, arteriography allows us to select the most appropriate artery and we are loath to rely on Doppler alone Furthermore, in a severely ischaemic leg we have had difficulty finding any audible signal but have nevertheless performed a successful graft—we are therefore most interested in the technique of induced pulsation advocated by Beard and his colleagues (unpublished data).

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1 Campbell WB, Fletcher WL, Hands LJ. A study of distal lower limb arteries: a comparison of Doppler and arteriograms. *Ann R Coll Surg Engl* 1986, **68**: 37–9

Erratum

'Relationship between gastric emptying of liquid and postvagotomy diarrhoea', by N. J. Parr, S. Grime, S. Brownless, M Critchley, J. N Baxter and C. R. Mackie, *Br J Surg* 1988, **75** 279–282, page 280, Figures 1 and 2. Although the captions were printed correctly, the figures themselves were transposed, so that the caption to Figure 1 relates to the figure printed above the caption to Figure 2, and Figure 2 is printed above the caption to Figure 1. We apologize for this error

Book reviews

The Foot in Diabetes

H. Connon, A. J. M. Boulton and J. D Ward 235 × 150 mm. Pp. 168 + xii Illustrated. 1987 Chichester John Wiley and Sons Ltd £15.00.

This book is a compilation of contributions to a symposium held on the 'Diabetic Foot' in May 1986. There are 17 authors all from the UK covering a wide range of fields including medicine, radiology, chiropody, provision of footwear and general and orthopaedic surgery. The introduction rightly highlights the need for a multidisciplinary approach in the care of this difficult problem. A publication of this sort leads inevitably to repetition, contributions of varying quality and a failure to cover the issues systematically The best are of considerable interest and a useful source of comprehensive and up-to-date references. The less appealing chapters state the obvious and some are anecdotal. I found two areas particularly interesting. The first was on the assessment of abnormal foot pressure areas, the second on the inappropriate microcirculation in the diabetic foot.

Perhaps somewhat surprisingly there is little on reconstructive surgery, particularly as diabetics represent about one-third of patients undergoing arterial surgery for critical ischaemia. Indeed this area is considered by one author as 'not commonly useful'. This is unfortunate because the evaluation of patients who might benefit from reconstruction would have been of relevance and interest and is in itself worthy of attention and debate A tantalizing chapter on angioplasty and its value in dilatations below the popliteal artery is short of hard data. However, this may be the first of a number of volumes on this subject and the proceedings of next year's meeting may fill in some of these gaps. Is it worth buying? Yes, on balance I think it is because it addresses such a common problem which invokes the participation of practitioners of so many medical and paramedical disciplines to whom it would be of varying interest and value.

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A Colour Atlas of Omental Transposition for Advanced Breast Carcinoma. Volume 42

H. White. 265 × 195 mm. Pp 63. Illustrated. 1987. London Wolfe Publications Ltd. £19.00.

It is a new experience to review a book about a procedure I have never had to perform, although it has been useful on occasions to know that the omentum is available when required

Harvey White is a noble protagonist for the omentum so it is not surprising that he has undertaken this venture in the Wolfe 'Single Surgical Procedures' series The brief for this series, as I recall it, was to provide a volume which enabled the procedure to be performed by an inexperienced surgeon. Mr White's book contains some useful hints for the experienced practitioner but I suspect the tiro will soon be lost (and the pedicle with him) The illustrations for the most part show what is intended and, with one or two exceptions, are of good quality. The line drawings of the omentum seem to highlight the peritoneal reflection while *Figures 3* and *6* could have been usefully placed adjacently *Figures 7–13* fascinated me but I fear will not help the jobbing surgeon perform better

I have a few other quibbles: for example, most of us do not have lasers. I prefer to do the destructive surgery first and then see what the remaining options for reconstruction are and I would emphasize the need to develop a wide and loose tunnel for the pedicle. The technique of delayed primary grafting could be used with benefit in this situation. The section on special situations is rather superfluous as all these operations tend to be one off and each case presents its own special challenges which do not really permit generalizations.

In spite of its drawbacks and limited application, the technique deserves to be better known than it is and the presence of this volume in the popular Wolfe Series should enable a wider audience to be reached

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Exocrine Pancreatic Cancer

H. Baumel and B Deixonne. 168 × 245 mm. Pp. 207. Illustrated. 1986 Berlin: Springer-Verlag. DM 168.00

Professor Baumel and Dr Deixonne, and their co-authors, have attempted to review the entire subject of pancreatic cancer from epidemiology and pathology, through radiology and diagnosis, to attempts at cure and palliation. Most of the diagnostic and treatment possibilities are discussed and the authors explain their approach to these tumours.

Unfortunately many of the arguments in this book are lost in language which is often quaint, 'retentional jaundice' and masses which 'transmit aortic throbbings', or phrases such as 'anatomoclinical parallelisms' which are clumsy and difficult to follow Even when comprehension is easy it is difficult to accept some of the arguments, for example the significance of an epigastric bruit or the use of CT scanning to diagnose gallstones

The chapter dealing with the pathology of these tumours is well written and emphasizes the different histological types of pancreatic cancer Similarly, the chapters on radiology and diagnostic strategies discuss the pros and cons of the many imaging techniques now available and give clear guidelines for investigating patients suspected of having pancreatic pathology.

Although all forms of treatment are discussed the authors' enthusiasm for radical surgery, including, rarely, resection of hepatic metastases, gives a biased account of the surgical management. Little attempt is made to separate periampullary tumours from tumours of the rest of the gland in analysing the results of surgery. It is also a pity that the hormone responsiveness of pancreatic tumours and the implications this may have for therapy are not mentioned

A book of this type has a lot to offer the clinician, pathologist, radiologist and researcher but, until the text is made more comprehensible and the discussion more balanced, it is difficult to recommend this particular volume.

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Vivas in General Surgery

F G. Smiddy 215 × 135 mm Pp 330 + vi. Illustrated. 1987. London Blackwell Scientific Publications Ltd. £12.95

When I first picked up this book I thought it was going to be the answer for revision especially for the final fellowship general surgical vivas The cover is extremely eye catching but the very first question it poses, 'What is this book about?', has an incorrect answer The answer given is the heuristic method of clinical analysis. I had not come across this term before and was pleased to find it in the authors' preface. However, in checking in the dictionary I discovered that the heuristic method is not one in which diagnostic hypotheses are tested out one after the other as stated, but is defined as a system of education under which the pupil is trained to find out things for himself

The author states that the book can be used in two ways firstly for revision, and I will accept this usage although obviously not everyone will answer the questions the same way as the author However, he states that the book alternatively can be used as a simple text book, and with this I would take issue. It would be wrong for any serious student of general surgery to accept this as a text book. Although gastroenterological problems are well covered in 20 of the 33 chapters, the rest of general surgery received rather short shrift I also found these first 20 chapters rather pedestrian whereas the last 13 were much more crisp and exciting.

To read the book straight through as a text book was not easy and I found it much more useful on a second reading to pick it up and read a chapter on its own. Nevertheless, the short answers rarely contained sufficient detail, which proved frustrating as a revision text Surprisingly, there were very few answers that I would find unacceptable. However, I did find annoying the repeated inclusion of every drug maker's name. I think the reproduction of ultrasound is, in the main, unhelpful as this investigation is so 'operator dependent' and I would not expect surgeons in training to comment on these types of reproduction. I also found the number of spelling mistakes aggravating.

This book may prove popular with the surgeon in training in the midst of his FRCS examination having taken the papers before the vivas However, I think he would probably be better off revising from his own notes or a concise revision text book No doubt the catchy cover will ensure its sale

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Reoperative Vascular Surgery

Trout 155 × 235 mm. Pp. 363 Illustrated. 1987. New York. Marcel Dekker. $89 00.

This is an excellent book and its publication will be a welcome and timely addition to the bookshelves of vascular surgeons in Britain The authors are practising clinicians from the Department of Surgery at the George Washington University Medical Centre They have selected 28 contributors from other parts of the United States, and cover the whole range of reoperative vascular surgery The first chapter on general considerations of reoperative vascular surgery is an overview of the state of the art. It produces an interesting number of statistics on the incidence of primary and reoperative vascular surgery in the United States and surveys the risk factors involved. I recommend this chapter to any surgeon in training.

The book then focuses on individual problems, covering the whole range of vascular surgery, from false aneurysms in the groin, graft infections, and reconstruction after axillofemoral bypass graft. The chapter by Ralph de Palma on reoperation for occluded aortic grafts deserves more than passing attention and there are worthwhile chapters on reoperation after femoropopliteal, femorodistal and *in situ* saphenous vein bypasses. Most surgeons would be tempted to skimp through the fairly lengthy treatment of reoperative surgery of the carotid artery but there is an interesting chapter on myocardial revascularization before peripheral vascular reconstruction. Other subjects dealt with include complications of dialysis access, microvascular procedures and operations on the inferior vena cava. The chapter dealing with recurrent varicose veins could have been much shorter Probably five contributors together felt they had to cover every possible point.

The book is well produced, there are good line drawings where needed and it is full of good, practical advice for the practical vascular surgeon.

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Principles of Surgical Technique

G. G Wind and N M. Rich. 280 × 210 mm. Pp. 280 + xii Illustrated. 1987 Baltimore· Williams and Wilkins. £29.25

This is a book dedicated to those surgeons who enjoy perfecting their surgical technique and passing on their skills to others. It deals at a basic level with all the aspects of tissue handling that the senior house officer commencing his career in surgery would be expected to learn. Essentially this book is aimed at the final year medical student and houseman and does not attempt to cover a wide range of specific operations. It covers hernia repair, cholecystectomy and arteriotomy but, as it states, it is not aimed at teaching aspiring surgeons how to perform specific operations but rather how to operate using the background of the history of the techniques of surgery and how to execute the critical fundamentals of aseptic techniques, tissue handling and haemostasis. These subjects are often overlooked.

This new second edition contains significantly expanded coverage of surgical staplers, wound healing and, surprisingly, micro-surgery· surprising because this book is aimed at relatively junior surgeons Painstaking line diagrams are used to illustrate the minutiae of technical points, almost to the point of obsession. The two authors, from Bethesda in Maryland, betray the difference in surgical training in the United States and England Great emphasis is paid to the way in which the junior resident would open the abdomen before the arrival of the consultant surgeon, this is not a practice that has been widely adopted in Great Britain. Nevertheless, this book is unique in that it does attempt to set down in pictorial form the principles that many junior surgeons struggle to absorb through observation and experience alone in the apprenticeship scheme of training

It is a pleasure to recommend this book to all those who are starting out on their surgical career. It should be carefully read before embarking on an anastomosis course. However, I doubt whether the established surgeon would find much benefit from it.

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Recent Advances in Urology/Andrology 4

W. F. Hendry 162 × 240 mm Pp. 336. Illustrated 1987. Edinburgh Churchill Livingstone. £45.00

The *Recent Advances* books occupy a place in between original articles and standard textbooks. The success of such books depends on the skill of the Editor in choosing firstly the subject matter and secondly authors of calibre who are experts in the fields chosen. In this book Mr Hendry has chosen wisely on both counts, for the chapters cover a wide range of subjects from radiological imaging to radical surgery and the authors are all acknowledged experts in their fields. Inevitably the chapters vary in quality and appeal but everyone will find several chapters of great interest and I enjoyed reading most of them.

Selection of chapters on which to comment is difficult but those that particularly appealed included Michael Handley Ashken's masterly review of the Stamey procedure for stress incontinence, John Scott's comprehensive review of the present position of vesico-ureteric reflux (123 references—what a task!) which still leaves a large question mark over the condition, Giles Brindley's crisp summary of pharmacologically induced erections and the excellent chapter by Professor Michael Peckham and the Editor on testicular cancer.

Many of the views expressed are of necessity controversial and much of the material can be found, with diligent searching, elsewhere However, the book compresses much information into just over 300 easily read pages and has something for everyone practising urological surgery

Forty-five pounds (even a tax deductable forty-five pounds) is quite a lot of money for an individual to spend on a book which inevitably will date fairly rapidly, but I would regard it as an essential buy for every hospital and departmental library.

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Surgical Management of Morbid Obesity

W O. Griffin Jr. 150 × 230 mm Pp. 284 Illustrated. 1987 New York Marcel Dekker Inc. $95.50.

Surgery for massive obesity has changed rapidly over the past decade, new techniques or modifications of old ones evolving with almost a 'flavour of the year' frequency Thus, it is useful to have an up-to-date perspective of the 'state of the art' which this book provides. All the authors are well known contributors to the field who express considerable experience and valuable opinion. All the gastric restrictive procedures used over the past 10 years are described and beneficial and undesirable effects discussed. The currently popular and most effective techniques, gastric bypass, vertical banded gastroplasty and vertical silastic banded gastroplasty are assessed in detail, particular attention being devoted to nutritional and metabolic aspects. Horizontal gastroplasty and the even less successful anterior gastrogastrostomy, gastric wrapping, gastric partitioning, gastric balloons, vagotomy and gastric banding are briefly considered. Biliopancreatic intestinal bypass is the only intestinal short circuit procedure still in use and is discussed in considerable detail by its main proponents. The reader of the subject will realize why it is not popular elsewhere than in Italy. The importance of case selection of precise surgical technique and measurement as well as dietary management and regular follow-up are emphasized as a basis of success in whatever technique is employed. The book is an easily readable review which will be of particular value to those considering this type of surgery.

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Journal abbreviations

Acta Medica Colombiana [Acta Med Colomb]
Acta Orthopaedica Scandinavica [Acta Orthop Scand]
Acta Paediatrica Japonica [Acta Paediatr Jpn (Overseas)]
Acta Paediatrica Scandinavica [Acta Paediatr Scand]
Acta Pharmacologica Sinica [Acta Pharmacol Sin]
Activox [Activox]
AIDS An International Bimonthly Journal [AIDS]
AJR American Journal of Roentgenology [AJR]
American Family Physician [Am Fam Physician]
American Journal of Cardiology [Am J Cardiol]
American Journal of Clinical Nutrition [Am J Clin Nutr]
American Journal of Diseases of Children [Am J Dis Child]
American Journal of Emergency Medicine [Am J Emerg Med]
American Journal of Epidemiology [Am J Epidemiol]
American Journal of Hospital Pharmacy [Am J Hosp Pharm]
American Journal of Human Genetics [Am J Hum Genet]
American Journal of Medicine [Am J Med]
American Journal of Obstetrics and Gynecology [Am J Obstet Gynecol]
American Journal of Optometry and Physiological Optics [Am J Optom Physiol Opt]
American Journal of Pathology [Am J Pathol]
American Journal of Psychiatry [Am J Psychiatry]
American Journal of Public Health [Am J Public Health]
American Journal of Surgery [Am J Surg]
American Review of Respiratory Disease [Am Rev Respir Dis]
American Surgeon [Am Surg]
Anaesthesia [Anaesthesia]
Anaesthesia and Intensive Care [Anaesth Intensive Care]
Anesthesia and Analgesia [Anesth Analg]
Annals of Clinical Biochemistry [Ann Clin Biochem]
Annals of Clinical and Laboratory Science [Ann Clin Lab Sci]
Annals of Internal Medicine [Ann Intern Med]
Annals of Otology, Rhinology and Laryngology [Ann Otol Rhinol Laryngol]
Annals of the Rheumatic Diseases [Ann Rheum Dis]
Annals of the Royal College of Physicians and Surgeons of Canada [Ann R Coll Physicians Surg Can]
Annals of the Royal College of Surgeons of England [Ann R Coll Surg Engl]
Annals of Surgery [Ann Surg]
Annals of Thoracic Surgery [Ann Thorac Surg]
Annals of Tropical Paediatrics [Ann Trop Paediatr]
Archives of Dermatology [Arch Dermatol]
Archives of Disease in Childhood [Arch Dis Child]
Archives of General Psychiatry [Arch Gen Psychiatry]
Archives of Internal Medicine [Arch Intern Med]
Archives of Neurology [Arch Neurol]
Archives of Ophthalmology [Arch Ophthalmol]
Archives of Otolaryngology—Head and Neck Surgery [Arch Otolaryngol]
Archives of Pathology and Laboratory Medicine [Arch Pathol Lab Med]
Archives of Surgery [Arch Surg]
Archivos de Investigacion Medica [Arch Invest Med (Mex)]
Arizona Medicine [Ariz Med]
Arteriosclerosis A Journal of Vascular Biology and Thrombosis [Arteriosclerosis]
Australasian Journal of Dermatology [Australas J Dermatol]
Australian and New Zealand Journal of Medicine [Aust NZ J Med]
Australian and New Zealand Journal of Ophthalmology [Aust NZ J Ophthalmol]
Australian and New Zealand Journal of Surgery [Aust NZ J Surg]
Australian Family Physician [Aust Fam Physician]
Australian Journal of Hospital Pharmacy [Aust J Hosp Pharm]
Australian Orthoptic Journal [Aust Orthopt J]
Australian Paediatric Journal [Aust Paediatr J]
Bangladesh Journal of Child Health [Bangladesh J Child Health]
Bibliotek for Laeger [Bibl Laeger]
Biomedical Bulletin [Biomed Bull]
Boletin de la Asociacion Medica de Puerto Rico [Bol Asoc Med PR]
Boletin Medico del Hospital Infantil de Mexico [Bol Med Hosp Infant Mex]
Bordeaux Medical [Bord Med]
Brain and Development [Brain Dev]
British Dental Journal [Br Dent J]
British Heart Journal [Br Heart J]
British Homoeopathic Journal [Br Homoeopath J]
British Journal of Anaesthesia [Br J Anaesth]
British Journal of Industrial Medicine [Br J Ind Med]
British Journal of Occupational Therapy [Br J Occup Ther]
British Journal of Ophthalmology [Br J Ophthalmol]
British Journal of Pain [Br J Pain]
British Journal of Rheumatology [Br J Rheumatol]
British Journal of Surgery [Br J Surg]
British Medical Bulletin [Br Med Bull]
British Medical Journal [Br Med J]
British Osteopathic Journal [Br Osteopath J]
Bulletin of the Medical Library Association [Bull Med Libr Assoc]
Bulletin of the World Health Organization [Bull WHO]
Canadian Family Physician [Can Fam Physician]
Canadian Journal of Anaesthesia [Can J Anaesth]
Canadian Journal of Comparative Medicine [Can J Comp Med]
Canadian Journal of Public Health [Can J Public Health]
Canadian Journal of Surgery [Can J Surg]
Canadian Medical Association Journal [Can Med Assoc J]
Canadian Veterinary Journal [Can Vet J]
Cardiovascular Research [Cardiovasc Res]
Central African Journal of Medicine [Cent Afr J Med]
Cephalalgia [Cephalalgia]
Chest [Chest]
Chinese Journal of Anesthesiology [Chin J Anesthesiol]
Chinese Journal of Cardiovascular Disease [Chin J Cardiovasc Dis]
Chinese Journal of Dermatology [Chin J Dermatol]
Chinese Journal of Digestion [Chin J Dig]
Chinese Journal of Endocrinology and Metabolism [Chin J Endocrinol Metab]
Chinese Journal of Epidemiology [Chin J Epidemiol]
Chinese Journal of Experimental Surgery [Chin J Exp Surg]
Chinese Journal of Geriatrology [Chin J Geriatrol]
Chinese Journal of Hematology [Chin J Hematol]
Chinese Journal of Hospital Administration [Chin J Hosp Adm]
Chinese Journal of Industrial Hygiene and Occupational Disease [Chin J Ind Hyg Occup Dis]
Chinese Journal of Infectious Diseases [Chin J Infect Dis]
Chinese Journal of Urology [Chin J Urol]
Chinese Medical Journal [Chin Med J]
Chinese Journal of Internal Medicine [Chin J Intern Med]
Chinese Journal of Medical History [Chin J Med Hist]
Chinese Journal of Medical Laboratory Technology [Chin J Med Lab Technol]
Chinese Journal of Microbiology and Immunology [Chin J Microbiol Immunol]
Chinese Journal of Nephrology [Chin J Nephrol]
Chinese Journal of Neurology and Psychiatry [Chin J Neurol Psychiatr]
Chinese Journal of Neurosurgery [Chin J Neurosurg]
Chinese Journal of Nuclear Medicine [Chin J Nucl Med]
Chinese Journal of Obstetrics and Gynecology [Chin J Obstet Gynecol]
Chinese Journal of Oncology [Chin J Oncol]
Chinese Journal of Ophthalmology [Chin J Ophthalmol]
Chinese Journal of Organ Transplantation [Chin J Organ Transplant]
Chinese Journal of Orthopedics [Chin J Orthop]
Chinese Journal of Otolaryngology [Chin J Otolaryngol]
Chinese Journal of Pathology [Chin J Pathol]
Chinese Journal of Pediatric Surgery [Chin J Pediatr Surg]
Chinese Journal of Pediatrics [Chin J Pediatr]
Chinese Journal of Physical Medicine [Chin J Phys Med]
Chinese Journal of Physical Therapy [Chin J Phys Ther]
Chinese Journal of Plastic Surgery and Burns [Chin J Plast Surg Burn]
Chinese Journal of Preventive Medicine [Chin J Prev Med]
Chinese Journal of Radiological Medicine and Protection [Chin J Radiol Med]
Chinese Journal of Radiology [Chin J Radiol]
Chinese Journal of Stomatology [Chin J Stomatol]
Chinese Journal of Surgery [Chin J Surg]
Chinese Journal of Tuberculosis and Respiratory Diseases [Chin J Tuberc Respir Dis]
Chronic Diseases in Canada [Chronic Dis Can]
Circulation [Circulation]
Clinica Chimica Acta [Clin Chim Acta]
Clinical Chemistry [Clin Chem]
Clinical and Experimental Optometry [Clin Exp Optom]
Clinical Diabetes [Clin Diabet]
Clinical and Investigative Medicine [Clin Invest Med]
Clinical Pediatrics [Clin Pediatr (Phila)]
Clinical Pharmacy [Clin Pharm]
Clinical Preventive Dentistry [Clin Prev Dent]
Community Dentistry and Oral Epidemiology [Community Dent Oral Epidemiol]
Community Medicine [Community Med]
Cuadernos del Hospital de Clinicas [Cua Hosp Clin]
Danish Dental Journal [Dan Dent J]
Danish Medical Bulletin [Dan Med Bull]
Diabetes [Diabetes]
Diabetes Care [Diabetes Care]
Diabetes Journal [Diabetes J]
Diabetologia [Diabetologia]
Diagnostic Cytopathology [Diagn Cytopathol]
Drug Intelligence and Clinical Pharmacy [Drug Intell Clin Pharm]
Environmental Medicine [Environ Med]
European Heart Journal [Eur Heart J]
European Journal of Cancer and Clinical Oncology [Eur J Cancer Clin Oncol]
European Journal of Clinical Investigation [Eur J Clin Invest]
European Journal of Respiratory Diseases [Eur J Respir Dis]
European Journal of Rheumatology and Inflammation [Eur J Rheumatol Inflamm]
Family Medicine [Fam Med]
Family Practice Research Journal [Fam Pract Res J]
Finnish Medical Journal [Finn Med J]
Gastroenterology [Gastroenterology]
Gastrointestinal Endoscopy [Gastrointest Endosc]
Genitourinary Medicine [Genitourin Med]
Geriatrics [Geriatrics]
Gut [Gut]
Havana Medical Journal [Havana Med J]
Health Trends [Health Trends]
Hellenike Cheirourgike [Hell Cheir]
Hellenike Iatrike [Hell Iatr]
Hong Kong Medical Technology Association Journal [Hong Kong Med Technol Assoc J]
Hospital Pharmacy [Hosp Pharm]
Iatrike [Iatrike]
Indian Journal of Dermatology, Venereology and Leprology [Indian J Dermatol Venereol Lepr]
Indian Journal of Gastroenterology [Indian J Gastroenterol]
Indian Journal of Urology [Indian J Urol]
International Disability Studies [Int Disabil Stud]
International Journal of Epidemiology [Int J Epidemiol]
International Journal of Pediatric Nephrology [Int J Pediatr Nephrol]
International Surgery [Int Surg]
Israel Journal of Psychiatry and Related Sciences [Isr J Psychiatry Relat Sci]
JAMA [JAMA]
JNCI Journal of the National Cancer Institute [JNCI]
Journal of Allergy and Clinical Immunology [J Allergy Clin Immunol]
Journal of the American College of Cardiology [J Am Coll Cardiol]
Journal of the American Medical Association (See *JAMA*)
Journal of Applied Nutrition [J Appl Nutr]
Journal of Biological Standardization [J Biol Stand]
Journal of the British Association for Immediate Care [J Br Assoc Immed Care]
Journal of the Canadian Association of Radiologists [J Can Assoc Radiol]
Journal of the Canadian Chiropractic Association [J Can Chiropr Assoc]
Journal of Cardiovascular Surgery [J Cardiovasc Surg]
Journal of Chronic Diseases [J Chronic Dis]
Journal of Clinical Gastroenterology [J Clin Gastroenterol]
Journal of Clinical Pathology [J Clin Pathol]
Journal of the Danish Medical Association (see *Ugeskrift for Laeger*)
Journal of Diabetic Complications [J Diabet Compl]
Journal of Diarrhoeal Diseases Research [J Diarrhoeal Dis Res]
Journal of Epidemiology and Community Health [J Epidemiol Community Health]
Journal of the Faculty of Medicine Baghdad [J Fac Med Baghdad]
Journal of the Institute of Medicine [J Inst Med]
Journal of the Irish Colleges of Physicians and Surgeons [J Ir Coll Physicians Surg]
Journal of Laboratory and Clinical Medicine [J Lab Clin Med]
Journal of Maternal and Child Health [J Maternal Child Health]
Journal of Manipulative and Physiological Therapeutics [J Manipulative Physiol Ther]
Journal of Medical Ethics [J Med Ethics]
Journal of Medical Genetics [J Med Genet]
Journal of Neurology, Neurosurgery and Psychiatry [J Neurol Neurosurg Psychiatry]
Journal of Neuropathology and Experimental Neurology [J Neuropathol Exp Neurol]
Journal of Nuclear Medicine [J Nucl Med]
Journal of Nuclear Medicine Technology [J Nucl Med Technol]
Journal of Palliative Care [J Palliat Care]
Journal of Pathology [J Pathol]
Journal of Pharmacy Technology [J Pharm Technol]
Journal of Psychosomatic Research [J Psychosom Res]
Journal of the Royal Army Medical Corps [J R Army Med Corps]
Journal of the Royal College of Physicians of London [J R Coll Physicians Lond]
Journal of the Royal College of Surgeons of Edinburgh [J R Coll Surg Edinb]
Journal of the Royal Naval Medical Service [J R Nav Med Serv]
Journal of the Vivekananda Institute of Medical Sciences [J Vivekananda Inst Med Sci]
Lakartidningen [Lakartidningen]
Lancet [Lancet]
Leprosy Review [Lepr Rev]
Malaysian Journal of Pathology [Malays J Pathol]
Manedsskrift for Praktisk Laegegerning [Manedsskr Prakt Laegegern]
Medical Care [Med Care]
Medical and Pediatric Oncology [Med Pediatr Oncol]
The Medical Journal of Australia [Med J Aust]
Medical Laboratory Sciences [Med Lab Sci]
Medicina Clinica [Med Clin (Barc)]
Medicina Intensiva [Med Intensiv]
Medicine (Oxford) [Medicine (Oxford)]
Military Medicine [Milit Med]
The Mount Sinai Journal of Medicine [Mt Sinai J Med (NY)]
National Medical Journal of China [Chung Hua I Hsueh Tsa Chih]
Nederlands Tijdschrift voor Geneeskunde [Ned Tijdschr Geneeskd]
Neurology [Neurology]
New Doctor [N Doctor]
New England Journal of Medicine [N Engl J Med]
New York State Journal of Medicine [NY State J Med]
New Zealand Family Physician [NZ Fam Physician]
New Zealand Journal of Medical Laboratory Technology [NZ J Med Lab Technol]
New Zealand Medical Journal [NZ Med J]
Newfoundland Medical Association Journal [Newfoundland Med Assoc J]
Nigerian Medical Journal [Niger Med J]
No To Hattatsu [No To Hattatsu]
Nordisk Medicin [Nord Med]
North Carolina Medical Journal [NC Med J]
Nosokomeiaka Chronika [Nosokom Chron]
Nursing [Nursing]
Obstetrics and Gynecology [Obstet Gynecol]
Ophthalmology [Ophthalmology]
Otolaryngology and Head and Neck Surgery [Otolaryngol Head Neck Surg]
Papua New Guinea Medical Journal [Papua New Guinea Med J]
Pakistan Journal of Medical Research [Pakistan J Med Res]
Pathology [Pathology]
Pediatric Emergency Care [Pediatr Emerg Care]
Peritoneal Dialysis Bulletin [Perit Dial Bull]
Pharmaceutisch Weekblad [Pharm Weekbl]
Pharmaceutisch Weekblad Scientific Edition [Pharm Weekbl [Sci]]
Pharmacological Research Communications [Pharmacol Res Commun]
Pharmacotherapy [Pharmacotherapy]
Pharmacy Management Combined with the American Journal of Pharmacy [Pharm Manage Comb Am J Pharm]
The Physician and Sports Medicine [Physician Sports Med]
Postgraduate Doctor—Africa [Postgrad Doctor Afr]
Postgraduate Doctor—Asia [Postgrad Doctor Asia]
Postgraduate Medical Journal [Postgrad Med J]
Postgraduate Medicine [Postgrad Med]
Psychiatria Fennica [Psychiatr Fenn]
Public Health [Public Health]
Puerto Rico Health Sciences Journal [PR Health Sci J]
Quarterly Journal of Medicine [Q J Med]
Radiology [Radiology]
Revista Chilena de Pediatria [Rev Chil Pediatr]
Revista Clinica Espanola [Rev Clin Esp]
Revista de Gastroenterologia de Mexico [Rev Gastroenterol Mex]
Revista Espanola de Reumatologia [Rev Esp Reumatol]
Revista Medica de Chile [Rev Med Chil]
Revista Medica del Instituto Mexicano del Seguro Social [Rev Med Inst Mex Seguro Soc]
Revista Mexicana de Anestesiologia [Rev Mex Anestesiol]
Revista Mexicana de Radiologia [Rev Mex Radiol]
Salud Publica de Mexico [Salud Publica Mex]
Saudi Medical Journal [Saudi Med J]
Scandinavian Journal of Dental Research [Scand J Dent Res]
Scandinavian Journal of Haematology [Scand J Haematol]
Schumpert Medical Quarterly [Schumpert Med Q]
Schweizerische Medizinische Wochenschrift [Schweiz Med Wochenschr]
Sexually Transmitted Diseases [Sex Transm Dis]
Shinkei Byorigaku [Shinkei Byorigaku]
South African Medical Journal [S Afr Med J]
Southern Medical Journal [South Med J]
Springfield Clinic Medical Bulletin [Springfield Clin Med Bull]
Sri Lankan Family Physician [Sri Lankan Fam Physician]
Thorax [Thorax]
Tidsskrift for den Norske Laegeforening [Tidsskr Nor Laegeforen]
Transactions—American Society for Artificial Internal Organs [Trans Am Soc Artif Intern Organs]
Transfusion [Transfusion]
Tropical Gastroenterology [Trop Gastroenterol]
Ugeskrift for Laeger [Ugeskr Laeger]
Ulster Medical Journal [Ulster Med J]
Undersea Biomedical Research [Undersea Biomed Res]
Veterinary Radiology [Vet Radiol]
West Virginia Medical Journal [W V Med J]
Western Journal of Medicine [West J Med]
WHO Chronicle [WHO Chron]
World Health Statistics Quarterly [World Health Stat Q]
World Medical Journal [World Med J]
Yale Journal of Biology and Medicine [Yale J Biol Med]

This list is abstracted from: 'Uniform requirements for manuscripts submitted to biomedical journals'. *British Medical Journal* 1988, **296**: 401–5.

Notices and announcements

18–21 May 1988
Journées de Chirurgie Hépato-biliaire
Villejuif, France
Information. Professor H Bismuth, Hôpital Paul Brousse, 94804, Villejuif Cedex, France

20 May 1988
British Association of Endocrine Surgeons
Cardiff, UK
Information· Mr A.W. Goode, Honorary Secretary to the British Association of Endocrine Surgeons, Surgical Unit, The London Hospital, Whitechapel, London E1 1BB, UK

23–28 May 1988
Advanced Hepato-Pancreato-Biliary Surgery
Lund, Sweden
Information Professor Stig Bengmark, Box 5003, S-220 05, Lund 5, Sweden

29 May–3 June 1988
Second World Congress on Hepato-Pancreato-Biliary Surgery
Amsterdam, The Netherlands
Information Q. A. Laman Trip, Organizer, Alton House, Keizersgracht 792, 1017 EC Amsterdam, The Netherlands

8–11 June 1988
The Endocrine Society 70th Annual Meeting
New Orleans, Louisiana, USA
Information Dr D Lynn Loriaux, The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20814, USA

10–11 June 1988
3rd Steglitz Pediatric Surgical Symposium
Berlin, FRG
Information. Professor Dr J. Waldschmidt, Department of Pediatric Surgery, University Klinikum Steglitz de FU, Hindenburgdamm 30, 1000 Berlin 45, FRG

19 June–1 July 1988
Oral and Maxillofacial Surgery Course 855
Glasgow, UK
Information· Director, Courses Department, The British Council, 65 Davies Street, London W1Y 2AA, UK

20–22 June 1988
7th International Workshop for the Study of Vascular Anomalies
Hamburg, Germany
Information. Professor Dr D. A. Loose MD, Jurgensallee 44, Hamburg 52, FRG

24–25 June 1988
British Association of Surgical Oncology Summer Meeting
Stockton-on-Tees, UK
Information British Association of Surgical Oncology, Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

27–28 June 1988
Serotonin Explored: what it does and how it can be manipulated for therapeutic purposes
London, UK
Information. Miss Penny Robinson, IBC Technical Services Ltd, Bath House, 56 Holborn Viaduct, London EC1A 2EX, UK

29 June–1 July 1988
International Symposium on Therapeutic Progress in Urological Cancers
Paris, France
Information· Dr Saad Khoury, clinique Urologique (Pr Chatelain), Hôpital de la Pitié-83, Boulevard de l'Hôpital, 75634 Paris Cedex 13, France

3–9 July 1988
16th World Congress of the International College of Surgeons
Milan, Italy
Information Secretariat, Clinica Chirurgica III—Universitá degli Studi, Via F Sforza 35, 20122 Milan, Italy

6–8 July 1988
Tripartite Meeting: Joint Meeting of the Surgical Research Society, the European Society for Surgical Research and the Society of University Surgeons
Bristol, UK
Information Mr D J Leaper, Southmead Hospital, Bristol, UK

10–14 July 1988
XII Biennial Congress of the International Society of University Colon and Rectal Surgeons
Glasgow, Scotland, UK
Information· Dr H.S. Crum, Programme Chairman, Wick, Caithness, UK

14–16 July 1988
XIIIth International Update on Liver Disease
Royal Free Hospital, London, UK
Information Professor N. McIntyre, Academic Department of Medicine, Royal Free Hospital, Pond Street, London NW3 2QG, UK

14–19 August 1988
XII International Congress of the Transplantation Society
Sydney, Australia
Information Congress Secretariat, 145 Macquarie Street, Sydney, NSW 2000, Australia

28 August–1 September 1988
Fifth World Conference on Lung Cancer
Interlaken, Switzerland
Information Fifth World Conference on Lung Cancer, c/o AKM Congress Service, PO Box 6, CH-4005 Basle, Switzerland

30 August–2 September 1988
10th World Congress Collegium Internationale Chirurgiae Digestive
Copenhagen, Denmark
Information. Secretariat, Spadille Congress Service, Sommervej 3, DK-3100 Hornbaek, Denmark

4–8 September 1988
11th Annual Meeting of the European Neuroscience Association
Zurich, Switzerland
Information: 11th Annual Meeting of the European Neuroscience Association, c/o AKM Congress Service, PO Box, CH-4005 Basel, Switzerland

8–10 September 1988
Annual Meeting of the Association of Surgeons in Training
Belfast, UK
Information Mr Bernard Lee, Department of Surgery, Belfast City Hospital Tower, Lisburn Road, Belfast BT9 7AB, UK

10–18 September 1988
Fourth Annual Fall Ultrasound Symposia
London, UK
Information· Annual Fall Ultrasound Meeting, Medical Seminars International Inc, 21915 Rosco Boulevard, Suite 222, Canoga Park, California 91304, USA

12–14 September 1988
International Hepatobiliary Pancreatic Association
Nice, France
Information· Dr Jean Mouiel, Department of Surgery, Hôpital Saint Roch–BP319, 06006 Nice Cedex, France

14–16 September 1988
Royal College of Surgeons of England Annual Meeting of Fellows and Members
Cambridge, UK
Information Secretary, Royal College of Surgeons of England, 35/43 Lincoln's Inn Fields, London WC2A 3PN, UK

18–23 September 1988
The Second Oxbridge Organ Transplantation Course
Cambridge, UK
Information Director, Courses Department, The British Council, 65 Davies Street, London W1Y 2AA, UK

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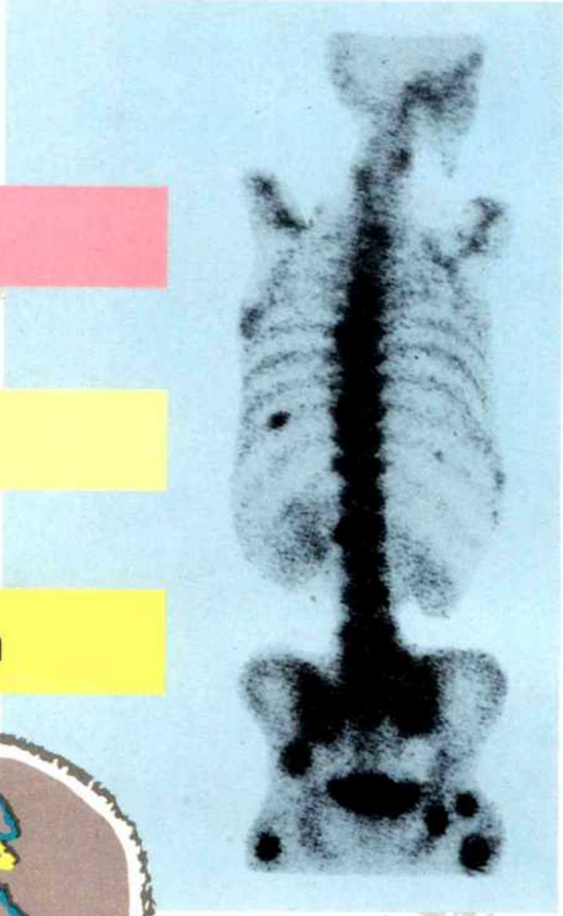

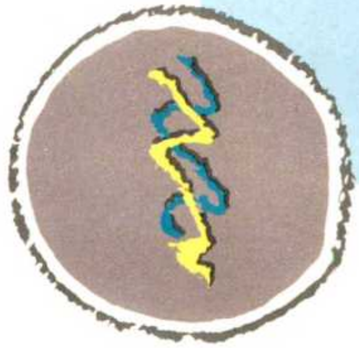

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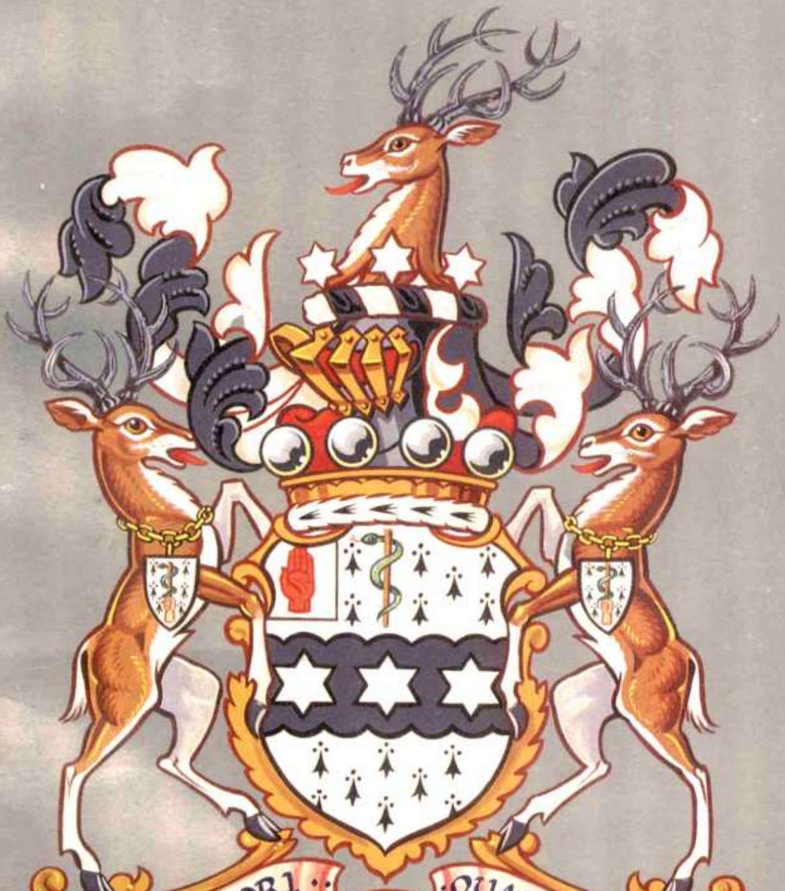
Volume 75, Number 6, June 1988



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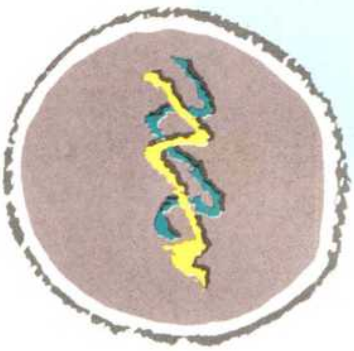

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Volume 75 Number 6 June 1988

Professor Hugh Dudley ChM, FRCS (Ed.), FRACS, FRCS 505
C. W. Jamieson

LEADING ARTICLE

Extracorporeal lithotripsy for gallstones 506
F. B. V. Keane and W. A. Tanner

REVIEWS

Dietary fibre and gastrointestinal disease 508
D. Cranston, D. McWhinnie and J. Collin

Hepatic metastases from colorectal cancer: resection or not 513
B. Greenway

Hepatic trauma: risk factors influencing outcome 520
R. Pretre, G. Mentha, O. Huber, P. Meyer, J. Vogel and A. Rohner

Tumour calcification following repeated hepatic de-arterialization in patients: a preliminary communication 525
S. Bengmark, B. Jeppsson, A. Lunderquist, K.-G. Tranberg and B. Persson

Pulmonary complications after subtotal oesophagectomy 527
M. Nishi, Y. Hiramatsu, K. Hioki, T. Hatano and M. Yamamoto

Carcinogenic potential of the non-cancerous epithelium in patients with oesophageal cancer 531
M. Maeta, S. Koga, N. Shimizu, Y. Inoue, M. Ishiguro and T. Sawada

Gastro-oesophageal reflux and intestinal malrotation in children 533
D. Kumar, R. J. Brereton, L. Spitz and Christine M. Hall

Lack of necessity for corrections for pyloric losses and duodenogastric reflux in the performance of gastric secretory studies 536
A. L. Ogilvie and M. Atkinson

Implication of duodenogastric reflux in the pathogenesis of Barrett's oseophagus 540
P. Gillen, P. Keeling, P. J. Byrne, M. Healy, R. R. O'Moore and T. P. J. Hennessy

Simple method of closing a para-ileostomy fistual (surgical workshop) 543
R. A. Greatorex

Mesenteric infarction: an analysis of 83 patients with prognostic studies in 44 cases undergoing a massive small-bowel resection 544
A. Sitges-Serra, X. Mas, F. Rogueta, J. Figueras and F. Sanz

Continuous enteral nutrition during the early adaptive stage of the short bowel syndrome 549
E. Levy, P. Frileux, S. Sandrucci, J. M. Ollivier, J. P. Masini, J. Cosnes, L. Hannoun and R. Parc

Plain abdominal radiographs and acute abdominal pain 554
J. P. M. Campbell and A. A. Gunn

Duodenal erosion complicating an implanted hepatic arterial access device (case report) 556
D. Cherqui, O. J. Garden and H. Bismuth

Effect of epidural analgesia on postoperative insulin resistance as evaluated by insulin clamp technique 557
I. Uchida, T. Asoh, C. Shirasaka and H. Tsuji

Permanent transrectal drainage of a diverticular-related abscess with a double-ended pigtail catheter (case report) 562
J. F. Chester, W. H. Turner, K. Lloyd-Williams and A. H. Chalmers

Tuberculous cervical abscess: comparing the results of total excision against simple incision and drainage 563
W. L. Chueng, K. F. Siu and A. Ng

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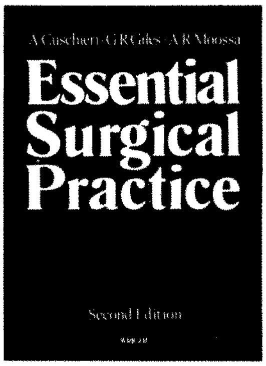
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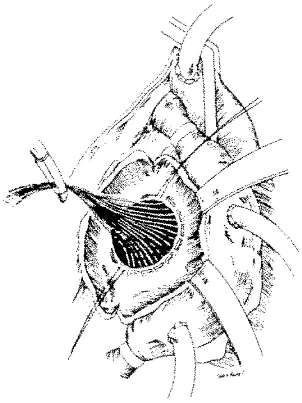

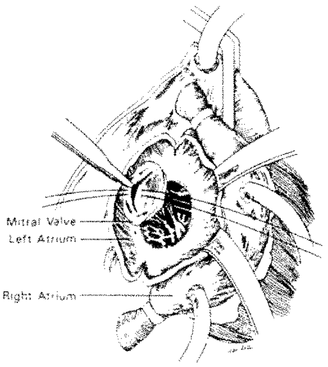

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Surgical management of substernal goitre 565
L. A. Michel and H. A. Bradpiece

Renal transplantation: the non-starters 570
T. W. J. Lennard, N. R. Parrott, R. G. Wilson, G. Proud, J. R. Farndon, Judy M. Simpson and R. M. R. Taylor

Percutaneous obliteration of a chronic duodenal fistula (case report) 572
A. Bianchi, C. Solduga and M. Ubach

Non-operative management of retroperitoneal fibrosis 573
P. M. Higgins, D. N. Bennett-Jones, P. F. Naish and G. M. Aber

Improvement of renal function in azotaemic hypertensive patients after surgical revascularization 578
C. A. Mestres, J. M. Campistol, S. Ninot, A. Botey, C. Abad, M. Guerola, A. Cases, L. Revert and J. Mulet

Separation of malignant cells during autotransfusion (short note) 581
R. F. Dale, R. M. Kipling, M. F. Smith, D. St. J. Collier and P. J. Smith

Experience with percutaneous aspiration of amoebic liver abscesses (short note) 582
E. N. Elechi

Conservative management of perforated duodenal ulcer (short note) 583
T. E. Keane, B. Dillon, N. H. Afdhal and C. J. McCormack

Artificial pancreas in the diagnosis and treatment of insulinoma: a report of five cases (short note) 584
H. Gin, P. Erny, J. Perissat, L. P. Doutre and J. Aubertin

Comparison of polyglactin 910 and nylon in skin closure (short note) 586
I. A. Goulbourne, S. J. Nixon, A. R. Naylor and J. S. Varma

Bile acid concentrations in the refluxate of patients with reflux oesophagitis 587
D. C. Gotley, A. P. Morgan and M. J. Cooper

Augmentation of lymphokine-activated killer cell activity in patients with gastrointestinal cancer 591
P. C. Sedman, C. W. Ramsden, T. G. Brennan, G. R. Giles and P. J. Guillou

Effect of LHRH agonist, Zoladex, on ovarian histology 595
Karen Williamson, J. F. R. Robertson, I. O. Ellis, C. W. Elston, R. I. Nicholson and R. W. Blamey

SURGICAL RESEARCH SOCIETY ABSTRACTS 597

CORRESPONDENCE 619

BOOK REVIEWS 622

NOTICES AND ANNOUNCEMENTS 624

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The older Moynihan

As a youth and young man Moynihan's charm and prodigious industry carried him forward, but almost cocooned him from his environment. The Great War experience changed that. He had been commissioned as a major in the Royal Army Medical Corps (T) in 1908 and in December 1914 he was mobilized and went to France as a temporary colonel and consulting surgeon. In Flanders he made an immediate impact; his personal knowledge of the provincial surgeons who were now in the Royal Army Medical Corps enabled him easily to advise and encourage them and his comradeship and leadership supplemented his undoubted clinical prowess. War brought great surgical challenges to him but above and beyond surgery, Moynihan was uniquely able at speechifying and found himself addressing recruiting meetings, encouraging factory workers and raising support for the war effort. Patriotic oratory was an important, scarce commodity.

Moynihan moved fast; he was a powerful force in the Rouen Army Medical Society guiding army medical practice and drawing British and French medical officers together. His clinical impact was immediate; by the end of 1914, he was advising extensive debridement of wounds and the 'hypertonic treatment' with saline thereafter. By the spring of 1915 he was writing about the pathology and outcome of penetrating wounds of the knee. He was a member of a working party which published a memorandum on bacterial infections of projectile wounds in 1915. He was mentioned in Sir John French's Dispatch of 31 May 1915. Moynihan's contribution to the technical surgery of war requires no more mention here; he returned to England, became Chairman of the Council of Consultants and was ultimately promoted to major general.

More important activities than surgery next occupied Moynihan's time; he was '... selected to proceed to America on a Special Mission.' Ostensibly, the mission was to advise the American Surgeon General and the American College of Surgeons about battlefield injuries on the Western Front, but the covert reason was to use Moynihan's bellicose oratory to build up enthusiasm in America for the War. Moynihan met with all his old friends, Drs William Mayo, George Crile and W. B. Coley, and he was awarded the honorary fellowship of the American College; his reply to the citation rehearses his patriotism and triumphalism and, perhaps, his agenda for the future. The key word was 'tyranny'. 'Prussian tyranny' was contrasted to the high moral purpose of the allies fighting for liberty. Similar speeches in Philadelphia, New York, Rochester and Washington, toasts to the King, George V, with Sousa conducting *God Save the King*, and a visit to the President at the White House are related by Moynihan in his correspondence. He seems to have enjoyed his migration from surgeon to public orator—did he now have political aspirations?

Moynihan was elected President of the Royal College of Surgeons in 1926; his encouragement of research led to the development of laboratories in Lincoln's Inn Fields and to the inauguration of the Buckston Browne Research Farm. This enhancement of the College research capabilities seems almost out of character with Moynihan's 'worker surgeon', or purely clinical, image. Why had he never settled into the research orientated academic practice he was now promoting? Perhaps the answer partly lies in an unpublished minute of a meeting between Moynihan and the Vice Chancellor of Leeds University, Sir Michael Sadler, on 22 May 1919: 'We discussed the psychology of Yorkshire and its lack of appreciation of science as such, its concern for the prosperous career, its comparative scorn for professors as such as contrasted with Scotland, its practical ability ... it became clear that the Yorkshire problem is different ... but Yorkshire may alter under the influence of education.' Was Moynihan himself trapped in this provincialism?

Moynihan's scrap books, with their press cuttings, invitations, menus and photographs, reveal his desire for public esteem. The photograph of himself *en route* to Canada is fixed alongside a hitherto unknown photograph of Lister making the same journey about 40 years previously (*Figures 1* and *2*).

Although carefully trying to preserve his public image, Moynihan became embroiled in controversy as he became older. He held strong views on work, education and '... giving to the State the very best that was in us.' He developed the habit of writing under a pseudonym to newspapers, and sometimes writing the reply in the same correspondence column himself! Modern jargon would credit him with a 'return to Victorian values', yet he and his widowed mother were the victims and the success of these values! He encouraged the extension of hospital provision throughout Yorkshire and promoted the concept of a health service although he was reluctant to see an extension of 'beaurocracy'. His great disappointment was his failure to be elected a Fellow of the Royal Society. The one demonstrable flaw in his public persona was when he wrote to *The Times* to protest at this.

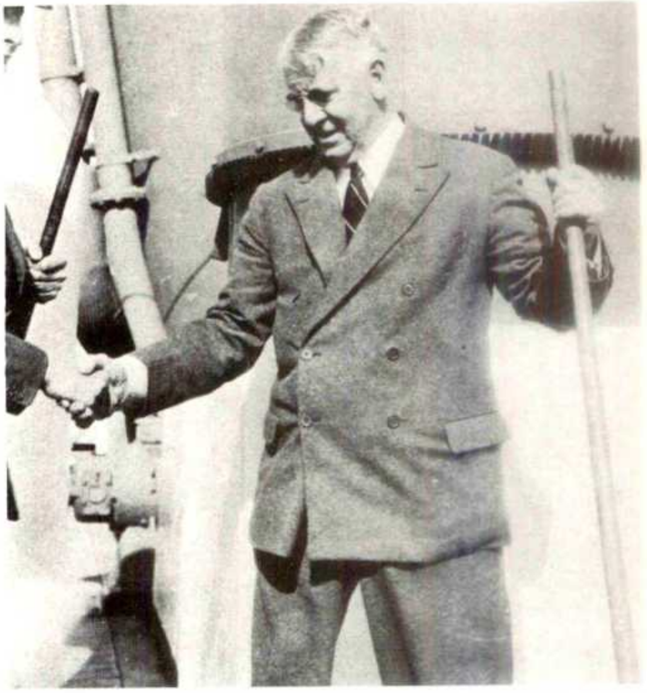

Figure 1 *Lord Moynihan playing shovelboard* en route *to Canada on the S.S. Duchess of York 1930*

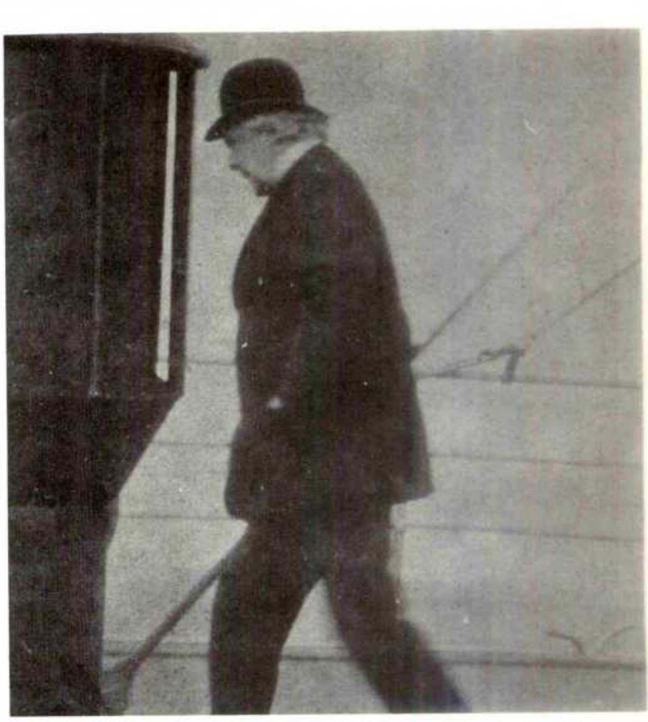

Figure 2 *Lord Lister playing shovelboard* en route *to Canada, 1897*

It is from such paradoxical behaviour that greatness is born. Moynihan stands with Billroth and Halsted for promoting the marriage of academic and clinical surgery, a marriage promoted to all surgeons in the United Kingdom and Empire by the founding of *The British Journal of Surgery* in 1913. Moynihan was created a Baron in 1929 and died 7 September 1937.

> 'Surgery has been made safer for the patient;
> we must now make the patient safe for surgery'.

From *Before and After Operation*, Harveain Oration delivered by Moynihan, 11 October 1926.

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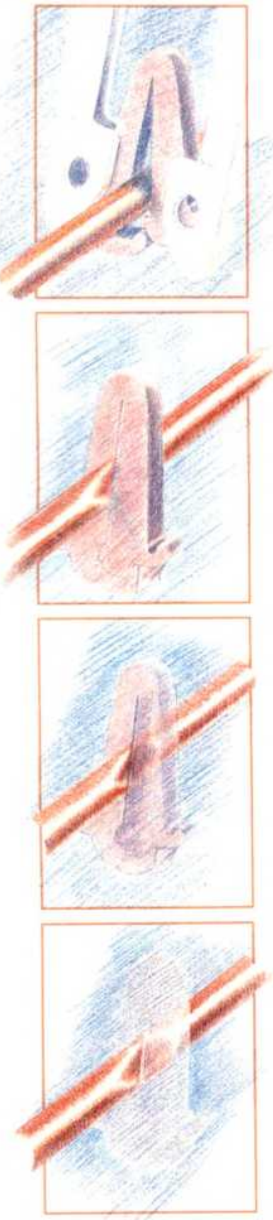

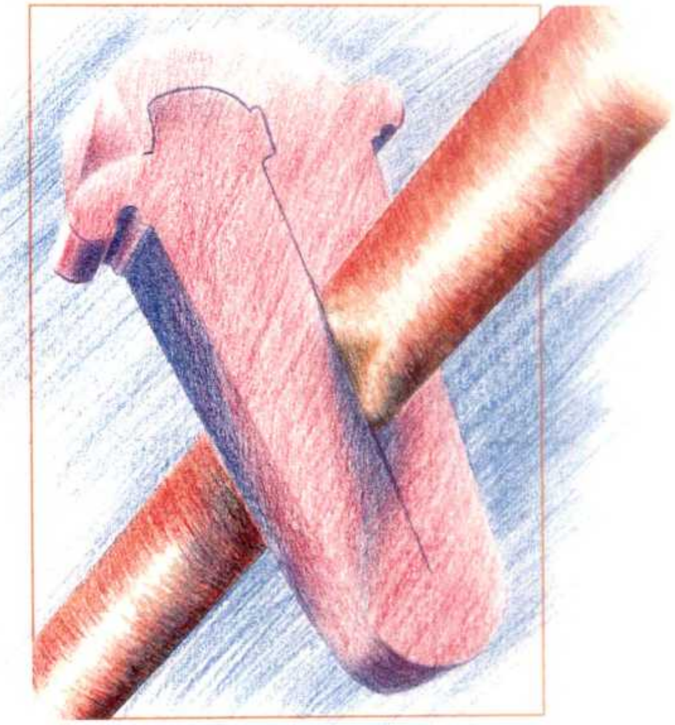

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The results of implantation studies of polydioxanone clips in animals indicate that the clips retained their strength longer than necessary for a thrombus or clot to occur in a vessel.

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Uses: ABSOLOK Extra clips are intended for use as absorbable ligatures. These clips are designed to offer a rapid, efficient means of ligation. Unlike cautery, the vessel and/or tissue is occluded with no thermal destruction. Unlike conventional metallic haemostatic clips, the absorbable clips are radiotransparent. Therefore, they will not interfere with interpretations of postoperative X-ray, CT or NMR scans.

The ABSOLOK Extra clip applier, designed for use specifically with ABSOLOK Extra clips optimises visibility of the clip at the ligation site and facilitates access to virtually all vessels and/or tissues.

Dosage and Administration: By implantation.

Contraindications, Warnings Etc: ABSOLOK Extra clips should not be used where prolonged or permanent ligation of tissues or vessels is required.

The use of the ABSOLOK Extra clip in vasectomy procedures and tubal ligation procedures is contraindicated. The safety and effectiveness of the ABSOLOK Extra clip in contact with neural tissues have not been established.

Use only with an ABSOLOK Extra clip applier of the appropriate size. Identification for each size is facilitated by the matching colour on the clip cartridge and the handle of the applier.

The clip must be latched to ensure proper ligation of the vessel or tissue.

Tissue must be compliant enough to allow latch to engage securely. Depending on the toughness of the surrounding tissue, the latch may not displace the tissue enough to latch. Some dissection of tissue from vessel surface may then be necessary.

As with any ligating device, the surgeon should inspect the ligation site following placement of the clip to ensure proper haemostasis and ligation has been achieved.

Do not re-sterilise the clips or clip cartridge.

Pharmaceutical Precautions: The recommended storage conditions are below 25°C, away from moisture and direct heat. Shelf life is 5 years, the expiry date is shown on each pack.

Legal Category: Not Applicable.

Package Quantities: Clips are available in four sizes as follows:

Product Code	**Colour Coding**	**Approximate Vessel Sizes**
AP100	Blue	0.5-2.0mm
AP200	White (silver handle on applier)	1.5-3.0mm
AP300	Green	2.5-4.0mm
AP400	Yellow	3.5-5.5mm

Each colour coded cartridge contains ten clips. Each cartridge is sealed in an aluminium foil pack and peel apart overwrap pouch. The sales unit is a filmwrapped box containing 6 packs.

Further Information: No clip related adverse reactions were reported during clinical trials.

Based upon the experience of the surgeon, ABSOLOK Extra ligating clips sizes and corresponding applier selection should be consistent with the vessel being ligated.

Closed clips have minimal gap ensuring even the smallest vessels in the appropriate size range will be properly ligated.

The latch of ABSOLOK Extra clips is designed to allow direct application to vessels with little or no tissue dissection.

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Reference Papers: ABSOLOK POLYDIOXANONE ABSORBABLE LIGATING CLIPS FOR SURGICAL LIGATION

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The Chairman

Professor Hugh Dudley ChM, FRCS(Ed.), FRACS, FRCS

Professor Hugh Dudley has completed his term of office as Chairman of The British Journal of Surgery Society and the Editorial Board. Past and present officers and members of the Editorial Committee unanimously agree that he has contributed greatly to the current relative stability and success of the Journal. He joined the Editorial Board in 1974, representing the Surgical Research Society, and was elected Treasurer of The British Journal of Surgery Society 2 years later. The Journal had existed in comfort, though without great distinction, since 1913 but the 1970s were troubled times for academic journals, owing to spiralling costs, modernization of printing methods and multiple amalgamations and collapses of publishing houses.

Professor Leslie LeQuesne, the Chairman, and his Editorial Committee relied greatly on Hugh Dudley's professionalism and experience of publishing in their efforts to trim costs and increase efficiency. These endeavours were a signal success and the Journal has never looked back. It grew slimmer and fitter, fertilized by the editorial skill and industry of the Editorial Secretary, Felix Eastcott.

Hugh Dudley was elected Chairman of the Journal in 1980, to face new battles. *The British Journal of Surgery* was at that time owned by an equal partnership of John Wright's, publishers, and The British Journal of Surgery Society Limited, comprised of elected representatives of the Editorial Board of the Journal. Each partner had the right to buy out the other if their relationship broke down. This, sadly, became the case and The British Journal of Surgery Society bought the title of the Journal from John Wright's, in an enforced sudden move, in 1983. This coup was engineered by Professor Dudley with firmness and tact. I am sure the Journal would be a shadow of its current stature had he not made this painful but necessary decision. His considerable expertise in publishing and high reputation amongst publishers were instrumental in the drafting of the current contract with our present publishers, Butterworths. The title of the Journal is owned solely by The British Journal of Surgery Society (and therefore by British surgery) which has the power to change publishers should it become necessary.

Since then the Journal has continued to expand under his leadership. It is now published in India and we hope that the Spanish edition will be in production this year. The number of editorial pages and their content has grown annually and there are plans for further expansion. New hazards loom on the horizon from declining investment in advertising in academic journals and continued takeovers in publishing houses, but we face them from a firm infrastructure created by Hugh Dudley and I shall hope to be able to call upon his advice throughout my term of office as Chairman.

There was understandable concern amongst some members of the Editorial Committee when Hugh's name was proposed as the new Chairman, that his reputation for incisive comment and even occasional intolerance of the foolish or inefficient would not ideally suit him to the post. *Who's Who* lists his hobby as 'accidentally and unintentionally annoying other persons', which does not help to instil great confidence in his potential role as a diplomat. These fears have, however, been unfounded. He has steered *The British Journal of Surgery* and its crew through many storms and we thank him on behalf of the Journal and the Societies which it represents—The Association of Surgeons of Great Britain and Ireland and the Surgical Research Society—for his unstinting diligence and devotion to the Journal.

C. W. Jamieson

Chairman
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Leading article

Br. J. Surg. 1988, Vol. 75, June, 506–507

Extracorporeal lithotripsy for gallstones

Cholecystectomy remains the corner-stone treatment for most patients with symptomatic gallstones. By and large it is a safe operation with little morbidity and very low mortality. It nevertheless involves considerable discomfort to the patient, a week of hospitalization and a month off work with all the attendant financial implications. For these reasons an array of technology-dependent alternatives to cholecystectomy are being explored. These include lesser surgical procedures such as percutaneous gallstone removal[1] or percutaneous gallstone dissolution with chemical solvents such as methyltertbutyl ether[2]. But perhaps the most significant challenge to cholecystectomy is coming from non-surgical approaches. This quest for non-operative treatment of gallstone disease has had a new lease of life since the advent of extracorporeal shock-wave lithotripsy (ESWL).

Chenodeoxycholic acid, ursodeoxycholic acid and terpenes either alone or in combination have been reported as effective methods of cholesterol gallstone dissolution but the criteria required for their use makes their application limited[3]. Not only does the gallbladder have to be functioning on oral cholecystography but the stones themselves should be of a non-pigment, non-calcified variety, < 1 cm in diameter and few in number. We have found that < 10 per cent of patients coming to cholecystectomy fulfil these criteria; even then the compliant patient after 1–2 years of treatment can expect, at best, a 60 per cent success rate. After all this, half of the successful patients will develop recurrent stones within 5 years.

As an adjunct to pharmacological dissolution of gallstones, ESWL offers theoretical advantages. As far as can be ascertained, ESWL cannot dissolve stones within the gallbladder but it can fragment them to smaller particles or to a sand. This may then be excreted by the gallbladder or be dissolved by oral agents, thus widening the spectrum of stones that are conventionally suitable for dissolution and also making that dissolution much more rapid. Ultrasound targeting, as opposed to radiological targeting, of the shock-waves has made the second generation lithotripters applicable to gallstone disintegration. Added advantages of these recently developed lithotripters are that they neither require the patient to be immersed in a water-bath nor do they require general anaesthesia, thus allowing treatment to be carried out as an out-patient procedure. However, just as there are theoretical advantages to lithotripsy so too are there anxieties concerning its use. The gallbladder is often a thin walled structure and therefore soft tissue injury to the gallbladder itself or to surrounding structures might be a potential hazard. Gallstones within the gallbladder are usually mobile and might bounce away from a focused shock wave making lithotripsy ineffective. Finally, fragmented particles might migrate and obstruct the biliary or pancreatic ducts giving biliary colic, jaundice or acute pancreatitis.

Paumgartner and colleagues from Munich have pioneered the development of ESWL for gallstones[4] and recently updated their experience in 175 patients treated for symptomatic lucent gallstones within functioning gallbladders[5]. There were solitary stones, < 30 mm in diameter, in 145 of their patients while the remainder had 2 or 3 smaller stones. Adjuvant treatment with a combination of chenodeoxycholic and ursodeoxycholic acids, was given to dissolve stone fragments. In patients with solitary stones, the stone had disappeared in 34 per cent by 2 months, in 84 per cent within 12 months and in all by 24 months. In patients with multiple stones the equivalent figures at each time interval were 13, 40 and 75 per cent. The side effects were generally mild and included cutaneous petechiae in 14 per cent of patients, transient haematuria in 3 per cent and mild pancreatitis in two patients. Attacks of biliary colic were suffered by 35 per cent of patients.

Clearly these are exciting results but, like all new techniques, ESWL for gallstones requires critical appraisal. Firstly, it would appear that only a small percentage of patients with gallstones are suitable for ESWL as the exclusion criteria are wide. Despite the initial expenditure on this expensive technology, lithotripsy as an out-patient procedure appears to be cost-effective when compared with surgery, although this has yet to be determined. Precisely which stones are suitable for ESWL also needs to be assessed as there are some stones that do not fragment easily. Calcium content gives some indication of difficulty of fragmentation and this may be measured

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radiologically or by CT scanning. The part played by oral dissolution agents as an adjunct to lithotripsy needs appraisal and, if indeed they are required, we need to know whether they are best given singly or in combination. The apparent paradox that lithotripsy of gallstones causes no significant soft tissue damage in the short term has been questioned[6]. Long-term damage also needs to be assessed carefully and continuously as studies proceed. Finally, and most importantly, we must know whether this form of treatment provides symptomatic relief and long term freedom from recurrence of gallstones.

Whereas it was deemed, albeit controversially, that ESWL treatment of renal stones should not be subjected to a controlled clinical trial[7], it seems that the many questions we have outlined demand that ESWL for gallstones does require careful clinical scrutiny. But these already difficult questions have been made more complex by the rapid appearance on the market of a variety of second generation lithotripters produced by different manufacturers[8]. Not alone do these lithotripters employ differing energy sources and focusing systems, but the shock waves they produce have different physical characteristics. As we do not understand the exact mechanism of stone fracturing by ESWL, some of these machines are probably more efficient than others while some probably cause more soft tissue damage than others. More work needs to be done before 'ideal' ESWL characteristics are defined.

We have to conclude that ESWL for gallstones offers exciting research and therapeutic possibilities and that further developments in this field are inevitable. However it is early days and cholecystectomy remains at present the correct treatment option for the vast majority of patients with symptomatic gallstones.

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W. A. Tanner

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Ireland

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Dietary fibre and gastrointestinal disease

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This review examines the evidence linking dietary fibre to gastrointestinal disease. Fibre increases stool weight, decreases whole gut transit time and lowers colonic intraluminal pressure. While it may be of benefit in the treatment of constipation, the irritable bowel syndrome and diverticular disease, its role in the prevention or treatment of other gastrointestinal disease has yet to be established.

Keywords: Diet, fibre, gastrointestinal disease

In the last 20 years it has been asserted that the consumption of dietary fibre is one of the hallmarks of a healthy lifestyle. It has been claimed that it offers protection against diverse diseases such as diabetes, coronary artery disease and obesity as well as the gastrointestinal (GI) disorders of constipation, gallstones, irritable bowel syndrome, diverticular disease, appendicitis, hiatus hernia and colonic carcinoma[1–3]. This article outlines the history of dietary fibre and critically reviews the scientific evidence for its role in diseases of the GI tract.

In the fifth century BC, Hippocrates wrote that 'white bread is more nutritious as it makes less faeces' while 'wholemeal bread cleans out the gut and passes through as excrement'[2] The Greeks and Romans had various grades of flour, but white bread was the most expensive and thought to be the most desirable. In Tudor England white bread was also a food of the rich, but it was not without its critics. In 1585 Stubs wrote that the poor man who ate brown bread, lived longer and was healthier than those who 'fare daintelie every day'[4]. In America, the 19th century physician, Sylvester Graham popularized wholemeal bread by writing a book on the importance of natural food[5]. In England, Queen Victoria advocated the eating of 'Graham bread' but it was still generally considered to be a poor man's food. The name 'Graham bread' is still retained in parts of the USA today. In 1885 Dr Thomas Allinson published *The Advantages of Wholemeal Bread*[6], but, although his ideas gained some public acceptance, he failed to convince the medical profession, partly because he also condemned many of the accepted medical treatments of the day. Ten years later he established a stoneground flour mill in Yorkshire for the production of a wholewheat bread which still bears his name.

Kellogg, in the earlier part of this century, spoke in favour of the value of whole cereal foods and suggested the use of bran[7], but his was an uphill struggle against men such as Alvarez who, as the leading American gastroenterologist of his day argued that man was carnivorous and that extra roughage was not beneficial[8,9]. Stimulated by Kellogg's ideas, Cowgill *et al.* found that eating bran doubled the stool weight and made defaecation much easier[10]. Fantus *et al.* investigating the role of bran as a colonic irritant, found that it caused a decrease in colonic mucus production[11]. In 1936 Dimock, in his Cambridge MD thesis entitled *The Treatment of Habitual Constipation by the Bran Method*[12], concluded that: 'Bran exerts a mechanical laxative action due to its fibre content, retaining moisture and allowing all the residues in the colon to resist dehydration'.

The origins of modern fibre theory began when Captain Cleave, medical officer of the battleship *King George V*, reported that raw millers' bran was an effective and inexpensive way of treating the constipation that troubled sailors at sea[13]. In 1956, he suggested that fibre depleted, refined foods were an important cause of disease in the western world[14]. His work concentrated on the adverse effects of refined carbohydrate in white flour and sugar, and Cleave's books stimulated renewed interest in the role of dietary fibre and disease[15,16]. In 1960, Trowell's book entitled *Non-infective Disease in Africa* was the first to list the 'western diseases', alleged to be caused by an inadequate intake of dietary fibre[17]. In 1969, Burkitt published the first of a number[18–20] of papers relating the prevalence of certain diseases of western civilization to a fibre depleted diet. Burkitt based his hypothesis on his experience as a surgeon in Uganda and on epidemiological evidence collected from hospitals throughout the Third World. In 1972 Painter *et al.* showed that an increased intake of fibre in the diet was beneficial in the management of diverticulosis, a disease that had previously been treated by low residue diets[21,22], and thus the modern era of the high fibre diet was established.

What is dietary fibre?

In 1972 Trowell defined dietary fibre as 'the remnants of plant cell material which are not digested by the human alimentary tract enzymes'[23]. This definition has been expanded to include various gums, such as guar gum, not normally present in the diet but used as food additives. The important sources of dietary fibre are cereals, fruit and vegetables. Wheat bran has 40–50 per cent fibre content; wholemeal bread 8·5 per cent; wheatmeal bread 5 per cent; and white bread 2·7 per cent.

Fibre affects the physiology of the GI tract in various ways. Because of their greater bulk, high fibre foods need more chewing and stimulate the production of more saliva. The increased mastication required and the greater volume of food, tend to reduce total calorie intake. In the stomach, gastric acid is buffered longer while the slower passage of soluble nutrients into the small bowel extends the absorption of sugars over a longer period.

There is now strong evidence that fibre together with starch which escape digestion in the small intestine are the principal substrates for fermentation in the large bowel. Therefore, they should be considered as two major determinants of colon function in humans[24]. Fermentation of carbohydrate results in lowering of the pH in the caecum and the production of short chain fatty acids. One of these, butyric acid, may protect the epithelium of the colon from dysplastic change[24].

It would appear that there are two distinct mechanisms by which fibre affects the human colon. Firstly, it stimulates microbial growth due to digestion of fibre sources such as apple, carrot and pectin[25] by bacteria. Secondly, wheat fibre remains largely undigested and retains water in the gut lumen[26]. The water retaining properties of fibre cause the stool to be both bulkier and softer. Thus bowel transit time is decreased, and colonic pressure lowered

Stool output and transit through the gut correlate positively with faecal bacterial mass, but negatively with colonic disease (which is more common in people with small stool outputs and slow transit times). The large intestine contains a mixture of bacteria, of which 99 per cent are anaerobic. It has been estimated that between 40 and 55 per cent of stool mass is due to the bacteria present[27]. Control of colonic microflora is thought to be of importance in determining the disease susceptibility of individuals[28].

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Constipation

Constipation is a disorder characterized by the passage of small amounts of hard faeces infrequently and with difficulty. It is often associated with a feeling of inadequate emptying on defaecation. Of the adult population of the UK, 1 per cent consult their general practitioner each year with the symptoms of constipation, an annual total of 400 000 consultations[29]. Up to 10 per cent of people consider themselves to be constipated, or have to strain at stool[30,31]. In a survey of 1445 healthy Britons of all ages, 99 per cent reported they defaecated at least three times a week[30]. In Britons over 60 years of age, the whole gut transit time is usually >72 h[32] and in some it may be >2 weeks. Daily stool weights in healthy young British adults have been measured as 111±33 g in women and 142±55 g in men[33] (mean ± s.e.m.). A diet high in fibre produces bulkier stools, with more rapid transit times[34]. Cranston and Burkitt found stool weights averaged 520 g and transit times 40 h in rural Kenyans on a diet of maize, beans and mashed bananas[35]. Similar observations have been made in Uganda[34] and India[36].

It is not unusual for all the symptoms of constipation to be cured by the addition of fibre to the diet[37]. Additional fibre is said to reduce the need to strain at stool and to increase the subjective feeling of complete emptying[21]. The effects of different forms of fibre on stool bulk vary greatly[38], with 20 g of bran fibre supplements leading to an increase in daily stool weight of 127 per cent while the same amount of fibre from guar gives only a 20 per cent increase. This is thought to be due to the capacity of the different forms of fibre to hold water and to the extent of fibre metabolism in the colon.

An increase in the fibre content of the diet usually relieves the symptoms of constipation, softens hard stools[39] and reduces straining and any feeling of incomplete emptying. This has been demonstrated in elderly patients in whom the ingestion of 15–25 g wheat bran each day for only 1 week lessened the requirement for an aperient[40]. A similar finding was reported with 100 elderly patients given 10 g fibre as a bran biscuit[41]. Institutionalized patients are a high risk group for constipation and, in a 12-month prospective study of such patients (average age 83·5 years) a daily dietary fibre intake of 25 g per person, was sufficient to eliminate aperient use[42] Constipation is a multifactorial problem, and low fibre diets are not the sole cause. The Eskimos of the Arctic, and the Masai of East Africa seldom complain of constipation, although they live on a diet containing very little fibre. Moreover, high fibre diets and laxatives are not always successful in the treatment of severe constipation, and may make some symptoms worse[43]. Turnbull *et al.* at St. Mark's Hospital studied a group of 13 women, whose failure to defaecate was due to incoordination of the pelvic floor, and found that dietary and drug treatment designed to soften and increase the bulk of the stool proved ineffective[44].

Irritable bowel syndrome

The irritable bowel syndrome comprises the symptoms of recurrent abdominal pain, abdominal distension and altered bowel habit (often alternating diarrhoea and constipation). The syndrome is believed to be due to a disorder of gut motility[2].

Fibre has become the mainstay of treatment for the irritable bowel syndrome since Painter implicated a fibre deficient diet in 1972[45]. By 1975, 95 per cent of gastroenterologists replying to a postal questionnaire reported that they used a high fibre diet in treatment, usually in conjunction with antispasmodics and psychotropic drugs[46]. Symptomatic improvement after dietary supplementation with bran has been frequently reported[46–49], but the results of controlled trials on patients with irritable bowel syndrome are inconclusive. Manning *et al.* found a significant symptomatic improvement in patients who changed from a low to a high fibre diet[46] while Ritchie and Truelove found ispaghula husk to be more effective than bran when used in conjunction with drug therapy[50]. In only one[50] of three double-blind trials was dietary fibre shown to be superior to placebo in relieving symptoms of the irritable bowel syndrome[50–52]. Cann *et al.*[53] found that coarse wheat bran was no better than placebo for most of the symptoms of irritable bowel syndrome although its efficacy in constipation was confirmed. Electrical recordings from the colon have shown that the abnormal colonic myoelectrical activity seen in patients with irritable bowel syndrome persists despite prolonged treatment with bran[54].

Further doubt has been cast on the therapeutic use of bran in this condition in a recent double-blind cross-over study carried out in Copenhagen on 20 patients with irritable bowel syndrome. Although 30 g of wheat bran significantly increased the stool weight and shortened intestinal transit time, there was no significant effect on the symptoms of abdominal pain and distension[55].

Although additional dietary fibre is effective in treating the constipation associated with irritable bowel syndrome, its place in the treatment of the other symptoms of the condition is unproven.

Diverticular disease of the colon

Segmentation of the colon is the means by which the colon propels its contents forward. Painter *et al.* showed, by simultaneous pressure studies and cineradiography, that during normal segmentation movements of the sigmoid, pressure rises considerably[56]. Painter also demonstrated that excessive segmentation can cause intermittent obstruction of the colon which may produce severe pain. Furthermore diverticula appear during active contraction rather than passive distension.

There are two proposed mechanisms by which a low fibre diet may promote the development of diverticula. A small volume of faeces results in a small colonic diameter and, according to Laplace's law, a high intraluminal pressure which could cause herniation of pockets of mucosa through the colonic wall at sites of weakness. The sigmoid is the narrowest part of the colon and the most active in segmentation, which may explain why it is so prone to diverticula. When colonic content is sparse it is suggested that closed segments of colon may develop with an excessive rise of pressure within them and consequent mucosal herniation. These theories are not without their critics. Eastwood *et al.*[57] have suggested that GI transit time, stool weight and intraluminal pressure in patients with early diverticular disease are similar to those of patients without diverticular disease, leading to the suggestion that constipation and high intraluminal pressure may be a complication of diverticular disease, and not necessarily part of its aetiology. However it is not clear from this study how many of their 'normal' patients would go on to develop diverticular disease later.

Diverticular disease was rare in Europe in the 19th century[58,59], but has steadily increased in prevalence this century, except during the Second World War when white bread was unavailable and only the high fibre war time loaf was available. Autopsy and barium studies have demonstrated that diverticula are rare before the age of 30, but the prevalence rises with age reaching 50–75 per cent in those over 80. There are considerable geographical variations with a low prevalence of diverticular disease in Africa and Asia[21,34,58], while diverticular disease has exactly the same prevalence in black as white Americans[60,61].

A number of studies has compared the fibre intake of patients with diverticular disease to matched controls Brodribb and Humphreys[62] demonstrated that the fibre intake of patients with diverticular disease was lower than that of 80 control patients matched for age and sex. Others have reported a significantly higher intake of dietary fibre in subjects without diverticula and have shown that cereal fibre has a greater protective effect than fruit and vegetable fibre[63,64].

Until 1970 diverticular disease was treated with a low fibre diet, on the assumption that coarse residue would lodge in the diverticula, leading to stasis, inflammation and perforation. In

1972 Painter *et al.* treated 62 patients with a high fibre diet, and noted a dramatic relief of abdominal discomfort and increase in frequency of defaecation over a 22-month follow-up period[21].

Prospective clinical studies in patients with symptomatic diverticular disease provide some evidence of the efficacy of treatment with dietary fibre supplements. Plumley and Francis[65] treated 48 patients with bran biscuits for 6 months to 3 years, and found that 73 per cent of symptoms were satisfactorily controlled, including pain in 69 per cent of cases. Brodribb and Humphreys[62] demonstrated a similar beneficial effect in an uncontrolled trial, and later carried out a double-blind cross-over study to compare the effects of high fibre and low fibre crispbread. Brodribb found that symptoms and pain were significantly improved with the high fibre preparation[66], although other studies have not confirmed these findings[67].

Several studies have demonstrated that bran lowers intraluminal pressure in the sigmoid colon[62,68–70], but a similar decrease has been reported with placebo tablets[71]. There is some evidence to suggest that surgery is undertaken less frequently for the complications of diverticular disease in district general hospitals in the British Isles than was the case 20 years ago[72]. This suggests a further possible role for a high fibre diet in the prevention of the complications, although it has no role in the treatment of established complications which should be dealt with by conventional surgical methods. However, fibre may be beneficial in the postoperative period; there is evidence that, unless bran is given postoperatively, pressures in the colon remain high after sigmoid colectomy for diverticulitis[73]. Furthermore, Hyland and Taylor showed in a 5–7-year follow-up that 91 per cent of patients who previously had been admitted to hospital for the complications of diverticular disease remained symptom free on a high fibre diet[74].

All the epidemiological data indicates that diverticular disease is a disease of western civilization, and that it is associated with a low intake of dietary fibre. In addition there is good evidence that treatment of the established disease by an increase in dietary fibre relieves symptoms and improves the function of the colon.

Carcinoma of the colon

Carcinoma of the colon is the second commonest cause of cancer death in the UK but it shows a 20-fold variation in frequency worldwide, with an incidence closely related to economic development. Burkitt's[3,80,85] suggestion of a dietary factor in its aetiology is supported by the fact that migrant populations soon establish a risk of carcinoma equal to that of the society in which they settle, provided dietary habits are also altered There have been several theories linking diet to the development of colonic carcinoma, including a high cholesterol intake and a low fibre intake. Cruse *et al.* showed that dietary cholesterol is co-carcinogenic in animals (facilitating the development of carcinoma, but not able to initiate it) and suggested a similar role in man[75]. A statistical analysis of international data has suggested that a high cholesterol intake has a positive influence on the development of colonic carcinoma[76]. A report from the International Agency for Research on Cancer (IARC)[77], compared the dietary intake and faecal characteristics in population samples from two areas of Denmark and Finland with a fourfold variation of colon cancer incidence. Their findings showed that meat consumption was higher in the high risk areas, while there were higher intakes of dietary fibre and milk in the low incidence areas

There are several ways in which a fibre depleted diet might influence the development of colonic carcinoma. The contents of the colon include a number of potential carcinogens, either derived from the diet[78] or from endogenous sources, for example certain bile acids[79]. Fibre in the food will have the twofold effect of decreasing colonic transit time and diluting these dangerous faecal constituents[80]. The reduction of colonic transit time may reduce the time of mucosal contact with the carcinogen, although the IARC study found no such correlation[77]. Fibre may also modify the metabolic activity of intestinal bacteria which convert bile acids and sterols to reactive metabolites which may be carcinogenic. There is a significant difference in faecal bacteria (Bacteroides were more common, Eubacteria and enterococci less common, in the high risk area), but not in faecal sterol concentration between high and low risk populations[77]. Recently it has been suggested that fermentation of fibre in the colon leads to the production of a number of short chain fatty acids, including butyric acid. *In vitro*, butyrate prolongs doubling times and slows the growth rate of human colorectal cancer cell lines[81]; it would seem to be effective in stabilizing colonic mucosa as well as being an important fuel for colonic epithelial cells[24]. In addition total bile acid excretion shows a significant negative correlation with dietary fibre, and a positive correlation with the risk of carcinoma[82]. A further mechanism may be the binding of reactive metabolites by fibre in the bowel[77]. The binding of glycochenodeoxycholic acid, a reactive metabolite, correlates significantly with fibre intake[83].

A low dietary fibre intake is only one of a number of factors implicated in colonic carcinoma. A recent study by Walker *et al.* of four South African populations found that, in these different ethnic populations, colon cancer is associated more with a low faecal pH than with the level of dietary fibre intake[84].

Gallstones

In developed countries the prevalence of gallstones is much higher than in the Third World[85]. There is some evidence that adding bran to the diet can cause the bile to become less saturated. Pomare *et al.* gave 20–40 g bran a day to women with radiolucent gallstones, and after 6 weeks their bile was significantly less saturated with cholesterol[86]. This is in contrast to healthy young men given 30 g bran a day where no difference was demonstrated, but their bile was unsaturated at the outset[87,88]. One of the problems with these studies is that they have been of relatively short duration, over a period of a few months, and long-term effects are unknown. In animal models, gallstones have been induced by various semisynthetic diets, high in refined carbohydrates[89]. These stones do not appear if the diet contains fibre[90] and stones that have been induced in this way disappear if fibre is added to the diet[91]. While the limited experimental and epidemiological evidence supports the hypothesis that a fibre depleted diet predisposes to gallstones, the case is far from established.

Appendicitis and haemorrhoids

These diseases are common in developed countries and rare in developing countries[19,85]. A number of hypotheses have linked them to the lack of a high fibre diet; while there is evidence to support the role of fibre in the prevention and treatment of haemorrhoids[92–94], in appendicitis the evidence remains inconclusive

Adverse effects of a high fibre diet

In patients eating a diet high in fibre, impairment of absorption of minerals, especially calcium, iron and zinc, has been reported, and mineral rich supplements may occasionally be necessary in high risk groups[95,96], although Walker disputes this[97]. Drug absorption may be reduced by some types of dietary fibre[98]. Abdominal distension and flatulence is sometimes a cause of complaint, especially among the elderly. High residue foods may precipitate intestinal obstruction in the presence of a tumour. Volvulus of the sigmoid colon is more common in Africa than the West, but it is not known if this is due to a high fibre diet. The eating of wheat fibre is absolutely contra-indicated in patients with coeliac disease In general, it is unlikely that doubling the average daily intake of fibre from 25 g to 50 g a day will have any deleterious effect on health.

Discussion

The evidence shows that the addition of fibre to food or the substitution of non-refined for refined food, increases stool weight, decreases whole gut transit time, and decreases intraluminal pressure in the colon. In addition it may be of benefit in the treatment of constipation, irritable bowel syndrome and diverticular disease. In other diseases the case for the role of dietary fibre in prevention or treatment is based on association and has yet to be established by experimental or clinical research.

If a naturally fibre rich diet does protect against many diseases of the western world, it may do so in a number of ways. The rural diets of Africa and Asia differ greatly from the refined western diet. They are richer in carbohydrate, especially starch, lower in fat, especially saturated fat, contain less sodium and more potassium, as well as different proteins with different ratios of amino acids. The large number of variables in the diet make it difficult to devise experiments to test the hypothesis that in the disease change of western culture, a decrease in fibre associated with a rise in fat intake are the most important factors. In addition, most of the diseases which are considered to be due to an absence of dietary fibre develop over many years and tend to be chronic and recurrent.

Over the last decade a high fibre diet has received increasingly enthusiastic endorsement by doctors and the general public as the means of preventing many of the diseases associated with the western way of life. While the epidemiological association of many of these diseases with low dietary fibre intake is beyond doubt, it does not prove that the relationship is causative. Scientific evidence that a high fibre diet prevents the development of GI disease or cures established disease is incomplete. In the absence of such evidence, some of the claims made for the beneficial action of bran must be treated with caution.

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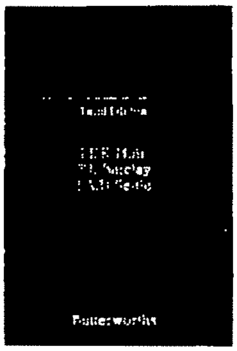

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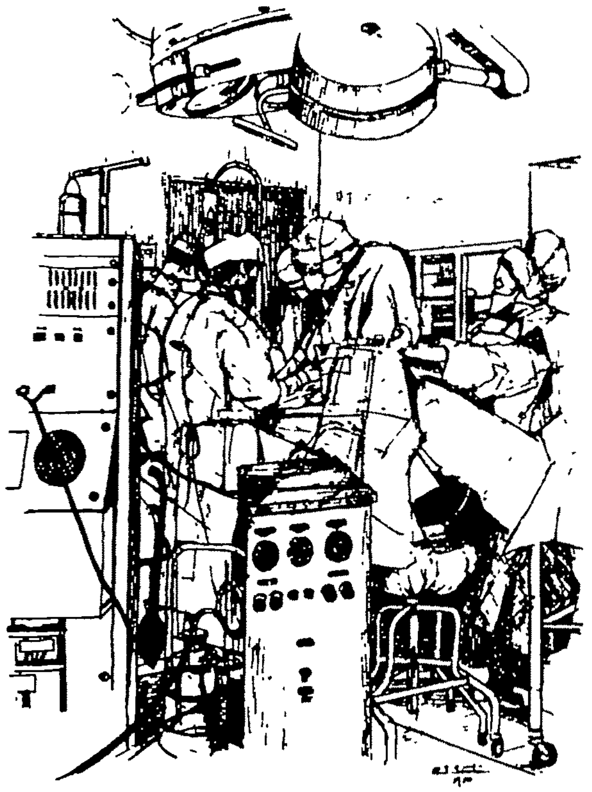

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Hepatic metastases from colorectal cancer: resection or not

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This review evaluates the available evidence dealing with the natural history of hepatic metastases in patients with colorectal cancer. Methods of detection of such metastases are discussed and the factors influencing survival after surgical resection are reviewed.

Keywords: Colorectal liver metastases, hepatic resection, recurrence rates

To consider excising a metastasis from the liver in a patient with colorectal carcinoma appears at first absurd. The tumour has escaped from its site of origin, and the host–tumour immune balance appears in favour of the carcinoma; the surgeon is contemplating a procedure which is apparently shutting the stable door after the horse has bolted. However, in a selected group of patients with metastases confined to the liver, about 25 per cent of those submitted to resection will survive for 5 years or more. Does the patient benefit from resection of the liver secondaries? To answer that question we must critically compare our surgical results with those obtained in patients with untreated liver metastases.

Survival in patients with untreated hepatic metastases

Hepatic secondaries from colorectal carcinomas are common. Between 15 and 35 per cent of patients have apparent or occult metastases at the time of their initial laparotomy (see below), while two-thirds of patients will have them by the time of their death[1]. Median survival time in untreated patients is between 4·5 and 15 months although some patients survive to 3 years and the occasional patient to 5 years. Spontaneous regression has even been reported[2].

Extent of liver involvement

It is clear from the reported series that survival is closely related to the extent of liver involvement by the tumour. Wagner *et al.*[3], in their careful retrospective analysis of 252 patients with biopsy proven secondaries, cited median survival rates of 10 months for widespread liver involvement compared with 15 months for multiple metastases confined to one side of the liver, and 21 months for those patients with solitary metastases. Furthermore, all of their patients with multiple unilateral or widespread disease were dead by 3 years, whereas 21 per cent of 39 patients with solitary lesions lived more than 3 years. Neilsen *et al.*[4] agreed with these findings in that after surgical assessment of the extent of liver involvement, patients with 'few' metastases had a median survival time of 18 months compared with 5 months for those with multiple lesions. Bengtsson *et al.*[5] documented an overall median survival time of 4·5 months in 25 patients, which on further analysis was 6·2 months in patients with <25 per cent involvement, and 3·4 months in those with 75 per cent or greater involvement. Jaffe *et al.*[6] reported a median survival time of 146 days in 177 patients with colorectal cancer; 56 patients with single metastases from a variety of gastrointestinal tumours had a median survival time of 136 days, while in a group of 229 patients with disseminated disease this figure is reduced to 72 days. Abrams and Lerner[7] reported a median survival time of 178 days in their group of 58 patients with hepatic metastases from colorectal cancer, 10 per cent of whom survived more than 2 years. Galante *et al.*[8] noted an 11·5 per cent 3-year and 5 per cent 5-year survival rate in their series of 74 patients. These last five series did not stress whether their patients only had hepatic metastases, a factor which Wagner *et al.*[3] had shown to be so important for accurate appraisal. Wood *et al.*[9], in their retrospective survey of 113 patients with liver involvement only, noted a mean survival time of 3·1 months for patients with widespread bilateral disease, compared with 16·7 months for those with solitary metastases. In Wood's[10] prospective series involving 101 patients he found that 73 per cent had widespread liver disease, 13 per cent had unilateral disease and 14 per cent had a solitary lesion; of the latter group, 16 per cent (2 patients) survived at least 5 years, while the majority of the patients in the other two groups were dead within 2–3 years. Goslin *et al.*[11] reported on 125 patients, 48 also having extrahepatic metastases; the median survival for the whole group was 12·5 months (1–59 months) The degree of hepatic involvement was assessed at presentation by technetium liver scan, and those patients with three secondaries or less had a median survival of 24 months compared with 10 months for patients with four or more lesions.

Importance of histology

The histology of the tumour may have some effect on the survival of patients with untreated hepatic metastases. Pestana *et al.*[12] noted that patients with well-differentiated liver secondaries survived twice as long as those with poorly differentiated lesions—11 months compared with 5·5 months. Others have agreed with these findings[6] and Goslin *et al.*[11] reported that the difference in their series of 125 patients was significant: those with poorly differentiated tumours had a median survival of only 6 months in contrast to 17 months for those with moderately well-differentiated histology, and 30 months for patients with well-differentiated metastases. Wagner *et al.*[3] only supported these findings in patients who had minimal liver involvement by metastatic disease. Neither Pestana *et al.*[12] nor Goslin *et al.*[11] took account of tumour volume in direct relation to the histological pattern.

Extent of surgery to the primary tumour

The effect of the extent of surgery carried out on the primary tumour in the presence of liver metastases has been considered by several authors. Abrams and Lerner[7], when comparing resection with bypass or no procedure, noted median survival times of 219 days and 65 days respectively. Neilsen *et al.*[4] supported this with mean survival times of 12·3 months with resection compared with 5 months without resection. Oxley and Ellis[13] also showed that patients having a bypass, colostomy or no surgical procedure fared less well than those having resection, although two patients with a bypass lived more than 1 year. Bengmark and Hafstrom[14], however, showed

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no difference between their resected or unresected groups, emphasizing that it was the degree of liver involvement which was the important prognostic factor. Furthermore, in the other quoted reports, it is likely that those patients with the more advanced disease had the lesser procedure. Undoubtedly, removal of the primary tumour will provide palliation, but it is the presence of metastases in the liver that ultimately determines survival.

Detection of liver metastases

So far, it is apparent that the degree of liver involvement by metastases is the prime determinant of survival, with the histological pattern probably being of minor significance. So how good are we, as surgeons, at detecting secondary spread as this may be the deciding factor in our decision to perform hepatic resection?

Liver metastases are found at laparotomy in 8–25 per cent of patients[5,8,13,14]. Unfortunately, it is clear that operative evaluation of liver secondaries is very inaccurate, the error possibly being as high as 50 per cent. Goligher[15], in an analysis of a consecutive series of 893 cases of rectal cancer, found surgically detectable metastases in 11·5 per cent of cases. Post-mortem examination on 31 patients who died postoperatively showed undetected secondaries in 5 Extrapolating this finding to the remaining 759 patients considered to have a normal liver, it is conceivable that a further 122 patients may have had hidden deposits, raising the level of hepatic involvement at initial laparotomy to 26 per cent. Finlay and McArdle[16], in a postoperative radiological analysis of 71 patients considered to be free of metastases at initial laparotomy, found that 17 (24 per cent) had occult secondaries which were confirmed on clinical follow-up. Hogg and Pack[17] (the latter an experienced hepatic surgeon) performed a post-mortem study of 100 patients with primary gastrointestinal tumours who were considered to be free of secondaries at laparotomy but who died in the postoperative period; they found that only 5 had occult liver metastases. Machi *et al.*[18], using intra-operative ultrasound, reported that 5 of 33 patients (15 per cent) had metastases which had not been discovered by palpation of the liver. If this range of figures for the incidence of occult secondaries is combined with those where liver metastases are discovered clinically at operation, it is clear that hepatic deposits are present at the time of initial laparotomy in from 15 to 35 per cent of patients.

Clinical examination of the liver at laparotomy is best performed bimanually, and the highest detection rates are probably achieved by more experienced surgeons. Metastases are often missed in Couinaud segments VI and VII[16], i.e. the more posterior aspect of the right lobe, which is an area that is difficult to assess accurately. Further difficulty arises if the right upper quadrant is the site of adhesions.

Pre-operative assessment of the liver by ultrasound or CT scanning, although not usually relevant to the primary procedure of excising the colorectal carcinoma, may, in experienced hands, detect deposits down to about 1 cm in size and occasionally down to 0·4 cm[16]. Detection depends on the echogenicity of the lesion, hypo-echoic tumours being more difficult to detect. The most encouraging recent development is that of intra-operative ultrasound, where metastases may be regularly detected to a size of 0·4 cm[18] so that colorectal carcinoma can be staged more accurately. This, in turn, can only lead to an improvement in our selection of patients deemed suitable for hepatic resection.

Resection of hepatic metastases

The first reported case of hepatic resection for metastatic disease was probably that published in 1888 by Garre[19]. Keen[20], in 1899, reviewed the literature of the past 13 years and noted several patients who had had hepatic resections for metastases from various gastrointestinal tumours. Cattell[21], in 1940, reported the successful case of a patient having an abdominoperineal resection for rectal carcinoma, and wedge resection of a solitary secondary from the right lobe of the liver. Lloyd-Davies[22] and Raven[23] both reported lobectomies on individual patients with colorectal primaries in 1947, the former patient surviving 2 years with no evidence of further secondary spread at subsequent post-mortem examination.

Since Flanagan and Foster's[24] pioneer review in 1967 of 72 patients surviving hepatic resection for metastatic cancer, an increasing number of centres are reporting small series of liver resections for colorectal metastases. Metastases from colorectal cancers are most often studied because they are common, tend to grow slowly, and originate from primary disease which can often be controlled by wide resection. So what are the variable factors with regard to the primary tumour, the number and extent of liver metastases and the extent of the hepatic resection which will enable some patients to survive for 5 years and very occasionally obtain cure?

Survival after resection (*Table 1*)

It is very apparent from the majority of reported series that patients with the fewest metastases survive longer after hepatic resection. Flanagan and Foster[24] reported a 23 per cent 5-year survival rate in 45 patients with secondaries from colorectal cancer. In a group of 72 patients with solitary or multiple hepatic metastases from a variety of primary tumours, 39 and 12 per cent 5-year survival rates, respectively, were observed. Attiyeh *et al.*[26] reported a 40 per cent 5-year and 28 per cent 10-year survival rate in 25 patients, 21 of whom had solitary and 4 of whom had multiple metastases (but with a maximum of 4). Wanebo *et al.*[27] reported a 28 per cent 5-year survival rate in 25 patients with solitary metastases, while Rajpal *et al.*[28] found a median survival time of 31 months in 30 patients with isolated metastases who survived operation, 15 of whom were free of disease at a mean follow-up of 23 months. Logan *et al.*[30] carefully analysed 19 patients: 12 had solitary lesions with a mean survival of 33 months, while 7 had multiple secondaries with a mean survival of 16 months. All patients with multiple secondaries were dead by 2 years. Iwatsuki *et al.*[31] reported 24 cases with a 40 per cent 5-year survival rate although they did not refer to the number of metastases. Taylor *et al.*[33] discussed 16 patients; the 3 patients with multiple metastases were all dead by 20 months. Using life table analysis of survival, those with single lesions had a predicted 42-month survival rate of 55 per cent. Kortz *et al.*[34] reported a 54 per cent 3-year and a 29 per cent 5-year survival rate in 16 patients with isolated metastases.

Fortner *et al.*[35] reported a series of 65 patients staged according to whether the disease was confined to the liver. Stage I tumours were confined to the resected portion of the liver without invasion of major intrahepatic vessels or bile ducts. The 37 patients with stage I disease had a 66 per cent 3-year survival estimate; 43 per cent of the 37 patients were disease-free. Of the 19 recurrences 17 were noted within 2 years. There was no difference in survival between patients with solitary or multiple secondaries, and the essential factor for successful treatment appeared to be removal of clinically evident disease, no matter how extensive the resection. Nims[36], in a study of ten patients treated at a community hospital, described six with single and four with multiple hepatic metastases. Nine patients were alive at 2 years. Tomás de la Vega *et al.*[37] reported a 33 per cent 3-year survival rate in 34 patients, with similar survival data in the 19 patients with single and 15 with multiple lesions. Their median survival rate figures were 31 and 33 per cent respectively. Cady and McDermott[38], in a thought-provoking paper, discussed 23 patients with metachronous metastases. They found a 40 per cent 5-year survival rate for patients having one, two or three secondaries, while those with four or more were all dead by 2 years. They also noted that this latter group had a shorter interval between resection and tumour recurrence. August *et al.*[39], in a series of

Table 1 *The survival rate after resection of hepatic metastases*

References (first author)	Year	No. of patients	No of patients with metastases		Median survival time	Five-year survival rate (%)	Ten-year survival rate (%)
			1–3 Metastases	>4 Metastases			
Woodington[25]	1963	7	-		3·1 years		
Flanagan[24]	1967	45				23	
Attiyeh[26]	1978	25	21	4*		40	28
Wanebo[27]	1978	25	25			28	
Rajpal[28]	1982	30	27		31 3 months		
Morrow[29]	1982	29	11	18		27	
Logan[30]	1982	19	12		33·2 months		
				7	15 8 months		
Iwatsuki[31]	1983	24				40	
Lim[32]	1983	7				(1)†	
Taylor[33]	1983	16	13	3			
Cady[38]	1985	23	18	5		40	
Kortz[34]	1984	16	16			29	
Adson[40]	1984	141				25	
Butler[42]	1986	62	42	20		34	21
Ekberg[44]	1986	72	35			24	
				37		9	

* Maximum figure; † one 5-year survivor

33 patients, 21 of whom had intraperitoneal 5-fluorouracil after liver resection, also found that patients with 3 or less metastases fared better than those with more than 4; the former patients had a median survival time of 44 months and 2- and 4-year survival rates of 86 and 59 per cent compared with a median survival time of 20 months, and a 2-year survival rate of 34 per cent with no 4-year survivors in the latter. Adson *et al.*[40], who have extensive experience of this problem, combined all of the previously published experience of the senior author in a report of 141 patients and found overall 3- and 5-year survival rates of 40 and 25 per cent respectively. There was no difference in survival between patients who had multiple lesions resected and those who had apparently solitary lesions excised. Petrelli *et al.*[41] reported on 31 patients who survived resection (22 patients having solitary and 9 multiple secondaries) and noted an overall 45 per cent 2-year survival rate which did not appear to be related to the number of metastases. Butler *et al.*[42] reported on 62 patients with up to 4 metastases and found 3-, 5- and 10-year survival rate figures of 50, 34 and 21 per cent respectively.

Gennari *et al.*[43] discussed 48 patients and, like Fortner's group, developed their own staging system. In 21 patients with stage I disease (single metastases involving less than 25 per cent of the liver) the actuarial 3-year survival rate was 73 per cent, of whom 28 per cent had recurrent disease within 2 years. In 9 patients with stage II disease (multiple metastases involving <25 per cent or single lesions involving between 25 and 50 per cent of the parenchyma) the actuarial 3-year survival rate was 60 per cent, while in stage III disease involving 18 patients (having either multiple lesions occupying 25–50 per cent, or metastases involving more than 50 per cent of the liver) actuarial 3-year survival was reduced to 29 per cent. All the latter patients had recurrences at 2 years. Ekberg *et al.*[44] reported on 72 patients, of whom 35 had single metastases. Of the 37 patients with multiple metastases, 26 had widespread deposits and 11 had one large secondary surrounded by small satellite lesions in the same segment of liver (probably representing intrahepatic dissemination by the portal vein). Five-year survival rates were 24 per cent for patients with solitary lesions, 9 per cent for those with multiple deposits and zero for those with large metastases plus satellite lesions. They, like Gennari, related survival to the amount of tumour within the liver, based on angiography. Those with a tumour volume of 25 per cent had a 5-year survival rate of 24 per cent, those with a 26–49 per cent tumour replacement had a 5-year survival rate of 7 per cent and no patients survived for 5 years with a 50–74 per cent tumour volume.

Table 2 *The extent of hepatic resection*

Reference (first author)	Year	Total no. of patients	TS	L	S + LLS	WR
Attiyeh[26]	1978	25		3	3	19
Rajpal[28]	1982	34	4	19	3	8
Logan[30]	1982	19	5	8	← 6 →	
Iwatsuki[31]	1983	19	1	11	6	1
Kortz[34]	1984	16	1	12		3
Fortner[35]	1984	65	14	42	9	
Cady[38]	1985	23		20		3
Adson[40]	1984	141	← 67 →			74
Gennari[43]	1986	48	3	19	26	

TS, trisegmentectomy; L, lobectomy; S, segmentectomy; LLS, left lateral segmentectomy, WR, wedge resection

Extent of resection (*Table 2*)

The extent of resection is dictated by the number, distribution and size of the metastases. Once allowance has been made for any increase in operative mortality with the more extensive resections, it is important to determine whether survival is affected. The terminology used in this review to describe the hepatic resections is that used by the authors.

Flanagan and Foster's retrospective review[24] noted that the overall survival rate figure of 39 per cent at 5 years following the lesser operations of wedge resection and 'partial lobectomy', compared quite favourably with more extensive resections. Other authors have also found that the simpler procedures offered a better median survival time[26]; Rajpal *et al.*[28] quote 48 months for wedge resection compared with 34 months and 25 months for right or left lobectomies respectively. However, as experience in hepatic resection has been gained, more extensive surgery has been performed with most recent authors reporting a very low operative mortality and excellent survival rates. Iwatsuki *et al.*[31] felt that extensive resection was justified based on a zero operative mortality rate, and 1-, 3- and 5-year actuarial survival rate figures of 91, 73 and 51 per cent respectively. Other authors have specifically related the extent of hepatic resection to the number of metastases present. Cady and McDermott[38], reporting on their series of 23 patients who had either lobectomy or wedge resection, divided them into those with 1–3 secondaries, and those with 4 or more. There was no striking difference in the size of resections between the two groups and they concluded that survival was related to the number of metastases and not the amount of liver removed. Gennari *et al.*[43] agreed with this, stating that it was the number and extent of liver metastases rather than the amount of liver resected that related to prognosis, as the extent of resection was tailored to the degree of liver disease. Their operative mortality was only 1 patient of 48 (28 had 'typical' lobectomies and 20 segmentectomies). Ekberg *et al.*[44] again noted that the type of liver resection did not influence survival but showed convincingly that it was the number of metastases that was so important—the cut-off figure being three or less. Adson *et al.*[40], in their major review, also noted that the extent of liver resection was not a significant determinant of survival, its significance only being related to operative mortality. Of 141 patients, 74 had simple wedge resection with no mortality, but nearly one-third required removal of half or more of the liver with a 4 per cent mortality rate. Overall 3- and 5-year survival rates were 40 and 25 per cent with no difference between patients having resection of solitary or multiple lesions.

Synchronous or metachronous metastases

It is very apparent from the literature that, as an isolated variable, the timing of liver resection in patients with colorectal metastases, whether conducted synchronously within about 3 months of the original laparotomy or metachronously, is of no prognostic significance. A number of authors[24,29,33,36,38,39,40,42,44] all make specific mention of this. Logan *et al.*[30], however, in their small series of 19 patients, noted a median survival time of 40·5 months in those patients in whom there was a delay of more than 2 years before the clinical appearance of their hepatic metastases, as opposed to 23·3 months in those with synchronous lesions.

Resection margin

Four authors have addressed the question of resection margin. August *et al.*[39] noted that disease-free survival was improved in patients with microscopically negative resection margins. Of 33 patients having a liver resection, 4 were found to have tumour involvement at the resection margins, all 4 having had multiple metastases; the median disease-free survival time for those with resection-negative margins was 16 months, and 7 months for patients where it was positive. All 4 had recurrent disease within 1 year ($P = 0·019$). Cady and McDermott[38] were more specific. Resected margins were measured grossly by the pathologist in the unfixed specimen, and were described as negative if there was 1 cm or more between the cut edge and the tumour and there was no microscopic involvement. Positive margins were those with < 1 cm between the edge and the carcinoma. Taking patients with the best determinant of survival (i.e. those with less than four metastases), of seven patients dead of disease six had positive margins with a median disease-free interval of 24 months (13–66 months) and a median survival time of 21 months (8–38 months). In 11 patients still living at time of report, all had negative margins with a median disease-free interval the same at 24 months (11–180 months), and a median survival time of 28 months (6–168 months). Ekberg *et al.*[44] further stressed the importance of a 1-cm resection margin and this was the only treatment variable that correlated with length of survival. For 27 patients with a margin > 1 cm, approximately 30 per cent survived 5 years, all of the 12 patients with a positive margin were dead by 31 months. The difference was significant ($P = 0·03$). Rajpal *et al.*[28] reported on their 30 patients: in 14 with a tumour-free margin of < 2 cm, the disease-free interval was 20 months and the median survival time 25 months. In 14 patients who had a > 2 cm margin, the disease-free interval and median survival time were both 51 months.

Dukes' classification of primary tumour

With regard to the significance of the Dukes' classification of the primary colorectal carcinoma and survival after hepatic resection, the reported series are about equally divided. A number of authors show no significant advantage[30,39,41,43,44]. However, in contrast, Attiyeh *et al.*[26] showed that 9 patients who originally had Dukes' A or B primary lesions had a median survival time after hepatic resection of 108 months, with 5 of 8 patients surviving more than 5 years, compared with 15 patients with Dukes' C lesions who had a median survival time of 24 months with only 3 of 12 patients surviving to 5 years. Morrow *et al.*[29], reporting on 29 patients (8 Dukes' B and 21 Dukes' C), noted that 5-year survival rate figures were 36 and 25 per cent respectively. In these two series the number of metastases was not related to the Dukes' classification, but 80 per cent of the patients of Attiyeh *et al.* had solitary lesions. Fortner *et al.*[35] noted that Dukes' classification was a significant variable in their survival analysis of 65 patients but made no note of the number of metastases. Butler *et al.*[42] again showed a significant survival advantage for Dukes' B compared with Dukes' C patients. The median survival time for B patients was 123 months with 47 per cent of 17 patients remaining disease-free, whereas those with C lesions had a median survival time of just 27 months with only 20 per cent remaining disease-free. All patients had less than four hepatic metastases. Adson *et al.*[40] noted that the difference in survival rates between Dukes' B and C patients was statistically significant.

Extra-hepatic metastases

The three studies that specifically mention extra-hepatic metastases note that their presence, whether nodal or visceral, is of grave prognostic significance. Adson *et al.*[40] found that when metastases to the diaphragm, adrenals, lungs, omentum or lymph nodes were removed at the time of hepatic resection, only one patient survived to 3 years and none to 5 years, compared with a 5-year survival rate of 30 per cent for patients without extra-hepatic metastases. Fortner *et al.*[35], using their staging system where stage III included lymph node and other intra-abdominal spread, described nine patients, none of whom had lived to 3 years at time of report, although five were still alive between 3 and 23 months. This compares with a 66 per cent 3-year survival estimate for their patients with stage I disease confined to the liver. Ekberg *et al.*[44] also noted a significant effect on survival. Of their 72 patients, 12 had extra-hepatic disease and their survival rate at 3 and 5 years was only 10 and 0 per cent, compared with 36 and 20 per cent when no extra-hepatic spread was found.

Pattern of recurrence after hepatic resection (*Table 3*)

A number of authors have studied this problem quoting hepatic or hepatic plus other organ involvement in between 30 and 60 per cent of patients[28,35,36,39]. They noted that hepatic resection often controlled the local disease, but that extra-hepatic recurrence developed relatively early after resection, usually within 2 years. Cady and McDermott[38] related recurrence to the number of metastases resected from the liver. Eighteen patients had one to three lesions, seven of whom had died, but only three had hepatic recurrence. Of five patients having four or more secondaries, all were dead, four with hepatic recurrence. Of the 48 patients reported by Gennari *et al.*[43], 22 had recurrences; all of their stage III patients had recurrence within 2 years and 28 per cent of their stage I patients at the time of report. The site of recurrence was liver only in ten, distant sites in seven, and liver plus distant sites in five. Butler *et al.*[42], reporting on their 62 patients, noted recurrences in 38, in 30 of whom the site was documented. Twenty (67 per

Table 3 *The pattern of recurrence*

Reference (first author)	Year	No. of patients	No with recurrence	HR	E-HR	HR + E-HR
Rajpal[28]	1982	30	11			11
Fortner[35]	1984	37*	18	5	13	
Nims[36]	1984	10	7		4	3
Steele[45]	1984	30	13	3		10
August[39]	1985	33	20	11		5
Cady[38]	1985	23	7	7		
Petrelli[41]	1985	36	21	3	4	14
Gennari[43]	1986	48	22	10	7	5
Butler[42]	1986	62	38	10	10	10

Some figures are not complete, and are as quoted by the authors. HR, hepatic recurrence; E-HR, extra-hepatic recurrence. * Stage I tumours

cent) had recurrence in the liver, ten of which were in the liver alone, while the other ten were associated with distant spread. The remaining ten were all in extra-hepatic sites. Steele *et al.*[45] reported 30 patients with 13 having recurrent disease, 8 of whom were still alive. In three patients the liver alone was involved, whereas in the remainder the recurrences were all extra-hepatic; all recurrent disease developed within 30 months. They stated that hepatic resection changed the proximate cause of death from liver failure to systemic disease. Hughes[46] collected data from 24 surgical centres in the USA and Europe on 899 patients who had undergone liver resection for colorectal metastases from 1948 to 1984. After discarding some records for various shortfalls, 607 patients who had had a 'curative' resection were evaluated. Recurrent tumour had developed in 424 patients (70 per cent); not all of the sites were documented but, of those available, the liver was a site of recurrence, either alone or as part of generalized disease, in 242 patients (43 per cent). Thus 57 per cent of patients did not have recurrent disease affecting the liver and, as Hughes has concluded, hepatic resection has taken a group of patients all of whom had hepatic metastases and achieved complete control of liver tumour in about half of them.

Discussion

We understand very little about the biological relationship that exists between the patient and his colorectal cancer. Some patients have a lightning course between diagnosis and death with widespread metastatic disease consuming them, while others appear to form a sort of commensal relationship with their tumour and survive for a number of years. We have to rely upon a knowledge of the histopathology and extent of disease as our only understanding of tumour biology at a specific time, so that suitable decisions can be made with regard to treatment. The pathologist can tell us the Dukes' classification of the primary tumour and its degree of differentiation which relates to its invasiveness and thus metastatic potential, and also crudely to its speed of growth; we as clinicians can determine the extent of metastatic spread. Unfortunately, our ability to assess the number and extent of hepatic metastases and degree of spread is still relatively crude. Only fairly large deposits, between 1 and 2 cm, which reflect many millions of cells may be regularly detected by ultrasound or CT scanning. Therefore we are unable to stage the tumour accurately in the majority of cases. It is this difficulty which is probably responsible for the fact that the majority of early recurrences become manifest within a year to 18 months. It seems likely that we simply did not detect the micrometastases responsible, and this contention is supported by the finding of unsuspected small deposits in hepatic resection specimens.

It is apparent that patients with solitary or up to three hepatic metastases are in a more favourable 'host–tumour balance' than those with four or more, as most reports, but not all, show a definite survival advantage for these patients after liver resection. Overall 5-year survival rate figures fall between 20 and 40 per cent, and up to 21 per cent may survive for 10 years. This is borne out by the fact that untreated patients with solitary liver metastases also have a longer mean survival time of 16–24 months, and up to 16 per cent survive to 5 years. This biological relationship, with the patient 'in balance' with his tumour for an extended period, is also attested by post-mortem studies where large, apparently slow-growing, solitary liver metastases appear to have been the cause of death—12 per cent in one series[38]. There is therefore a group of patients who only get liver secondaries and appear to exist in a relatively static state with their cancer, who would apparently benefit by liver resection with increased survival time and possible cure. Butler *et al.*[42] noted a 21 per cent 10-year survival rate in their 62 patients while Attiyeh *et al.*[26] noted 5 survivors at 10 years in their series of 25 patients.

These are the ideal patients, but there are patients with four or more metastases who may or may not be helped by liver resection. Such patients generally manifest recurrent hepatic and/or extra-hepatic spread within a year or so, and few survive for more than 3 years. It is impossible to know whether such patients have benefited in terms of increased survival time, but several authors have reported occasional 5-year survivors Adson *et al.*[40] have noted, in their patients with multiple secondaries (no number given), that those with large (>4 cm) multiple metastases have a better survival rate than those with multiple small (<4 cm) lesions, with 5-year survival rates of 37 per cent (in 18 patients) and 0 per cent (in 16 patients) respectively. It is interesting to speculate whether this result suggests that patients with multiple large metastases are more likely to be in a temporary state of balance with their tumour, and whether the showers of tumour emboli have stopped or the environment in which they are settling is in some way hostile, perhaps because of hormonal or immune factors.

If hepatic metastases are discovered at the initial operation and liver resection is considered a possibility at a later date, then a formal 'cancer curative' operation should be performed on the primary tumour to give maximum local control. Anything less should be discouraged as this may result in a high incidence of local recurrence despite successful hepatic resection.

The timing of resection of synchronous or metachronous metastases with relation to prognosis is evidently of no importance. Most surgeons do not resect synchronous metastases at the initial laparotomy, preferring to allow the patient to recover from one major procedure first. They then perform further investigations such as ultrasound, abdominal CT scan, pulmonary tomography and hepatic arteriography to clarify the position further. Resection is then usually performed within 3 months. Other surgeons wait for a specific time, usually 4–6 months in order to ascertain whether those metastases intially discovered are the only ones present, this 'waiting time' allowing for further growth of unrecognized micrometastases. This would appear to assume and hope that no further tumour embolization occurs during that period.

It is also apparent that the extent of liver resection is not related to survival, assuming the surgeon is experienced and has an acceptable operative mortality rate of <5 per cent, but is related to the number and size of metastases, and thus to tumour volume. Here again it appears that as long as there are less than four metastases, whether unilobar or bilobar, survival is not appreciably affected by the distribution or size of the lesions. Therefore, it is upon those patients with less than four hepatic metastases that we should concentrate our efforts, as advocated by Cady and McDermott[38] and Ekberg *et al.*[44].

The necessity for a clear resection margin of >1 cm, which has a significant survival advantage for the patient and reduces the likelihood of hepatic recurrence, follows the rules necessary for the successful resection of any tumour.

The pattern and timing of recurrence after liver resection is instructive. About 75 per cent of patients die within 5 years of recurrent disease (the majority within 3 years); over half of the recurrences are in extra-hepatic sites only, and patients do not apparently benefit from resection. The proportion of patients dying from undetected residual disease present at the time of liver resection is unknown, reflecting our inability to stage the tumour accurately. With improved methods of detection, such as intra-operative ultrasound, it is possible that we will be able to select patients more suitable for resection and improve 5-year survival rate figures. As Ekberg *et al.*[44] and Adson *et al.*[40] have demonstrated, there is very little survival advantage in resecting patients with extra-hepatic disease. These reported patterns of recurrence, of course, depend on the diligence with which clinicians and pathologists have sought out the exact sites of spread by clinical and post-mortem studies.

What of the future? It appears that the ideal patient for resection has a Dukes' A or B_1 tumour with well-differentiated histology, no more than three hepatic deposits and no extra-hepatic spread. Assuming he is operated upon by an experienced surgeon he has a 20–52 per cent probability of surviving to 5 years, which is much more favourable than that found in the untreated case fulfilling the same selection criteria. Even 20–40 per cent of patients with Dukes' B_2 or C lesions and poorly differentiated histology can survive to 5 years, as long as they have less than four metastases. Better staging is extremely important, and intra-operative ultrasound appears to be the ideal at present. Knowing that about 75 per cent of resected patients will get recurrent disease within 5 years, perhaps postoperative chemotherapy should be considered as August *et al.*[39] have noted a trend towards improved survival in their patients receiving intraperitoneal 5-fluorouracil.

The conclusion of this review is that hepatic resection for colorectal liver metastases definitely has a role in treatment. This has had to be based on the statement of Dr M. A. Adson quoted in Wagner *et al.*[3] that because enough is known about the natural history of untreated patients, 5-year survival rates can be used as evidence of surgical success. In all, 16 per cent of untreated patients with solitary liver secondaries will survive for 5 years, while up to 40 per cent of patients selected with less than four hepatic metastases will survive for 5 years after resection and 21 per cent for 10 years. In support of the conclusions of this review Wagner *et al.*[3] have demonstrated a statistically significant therapeutic effect for patients having a liver resection, compared with those having comparable disease but who were not resected for reasons determined by individual surgeons[47]. Unfortunately, they have shown that only about 7 per cent of all patients with liver metastases will benefit from such surgery.

Therefore hepatic resection for colorectal metastases should be considered by all clinicians, and particularly in those patients with the correct selection criteria as enumerated. As Adson has stated, 'Most patients who have malignant tumours cannot be saved by surgical endeavour; however, surgeons can do some good and should not give up trying, but they must evaluate their efforts in broad perspective because of the risk, pain, inconvenience, time and cost of such surgical procedures.'[47]. The benefits of the operation must be assessed carefully for each patient. In surgical liver units the expertise and necessary equipment have reduced the operative mortality rate to 5 per cent or less; thus it would appear that patients considered suitable for resection should perhaps be referred to such specialized units.

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Hepatic trauma: risk factors influencing outcome

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This retrospective study analyses the fate and associated risk factors of 99 patients who underwent laparotomy for hepatic trauma from 1977 to 1986. Blunt trauma (88 patients) and stab wounds (7 patients) had mortality rates of 36 and 14 per cent respectively. The overall death rate was 35 per cent. Multiple trauma patients had a significantly higher mortality for each additional system that was seriously injured. Pre-operative shock raised the mortality from 20 to 58 per cent ($P < 0·001$)*. For patients over 50 years of age, the mortality rate increased from 30 (younger patients) to 63 per cent* ($P = 0·028$)*. Minor hepatic wounds required relatively simple surgical measures in 60 patients, yet 13 died (22 per cent) of other causes. More sophisticated surgical management was applied to 27 major hepatic lesions, with 10 deaths (37 per cent). Twelve patients (seven with minor and five with major hepatic wounds) died before surgical treatment of the liver injury could be undertaken. The overall mortality rate of major hepatic wounds was 47 per cent and for minor wounds 30 per cent. However, the difference was not significant* ($P = 0·152$)*. Resection was resorted to in 15 patients, 5 of whom subsequently died (33 per cent). Classical hepatic lobectomy led to 4 deaths (50 per cent). Among the 35 deaths, 6 were due to the hepatic trauma itself (5 exsanguinations and 1 intra-abdominal sepsis). Isolated hepatic injury was fatal in three patients. We believe that conservative surgical measures should be used whenever possible in patients with hepatic trauma, especially when risk factors are encountered.*

Keywords: Hepatic trauma, risk factors

The steady increase in the incidence of hepatic trauma in our country is mainly due to the growing number of high velocity accidents. The mortality rate in these multiple trauma patients is depressingly high, especially if one considers that it usually affects young and previously healthy people[1].

The liver appears to be one of the most commonly injured organs in the abdomen[2–4]. Whereas the majority of hepatic lesions are relatively easy to manage, certain specific liver injuries continue to present a most challenging problem[5–10]. Reduction in the morbidity and mortality should be expected with the prompt identification of the various hepatic lesions and the correct choice of treatment[11–18]. The aim of this study is to review our 10-year experience with hepatic trauma and to identify those risk factors that influence the outcome

Patients and methods

We retrospectively reviewed 99 patients with hepatic trauma operated on in our hospital from 1 January 1977 until 31 December 1986. Most patients presented with blunt trauma, involving many systems. To gauge the gravity of blunt polytrauma, we routinely use the injury severity score[19,20] which assigns an index of gravity to the damage sustained by each of six assessed systems. This index, called the abbreviated injury scale (AIS), grades the severity of injury from a score of zero (minor) to five (critical) In the present study, we have considered as being severely injured any system assigned a score of three or more on the AIS

The hepatic injury itself was classified according to its operative management Lesions were either minor (repaired by simple means) or major (involving more sophisticated procedures like hepatotomy, hepatic artery ligation, perihepatic packing or hepatic resection) Although depending on the operator's judgment, this approach has been adopted because of the difficulty of accurately evaluating the extent of liver wounds on retrospective analysis and because of the current lack of agreement concerning hepatic injury classification[15,17,21–24]

Shock on admission was defined as a systolic blood pressure below 80 mmHg at any time before operation (discounting the transient drop provoked by anaesthesia induction).

Resuscitation was immediately undertaken in every patient presenting with severe trauma. Suspicion of abdominal bleeding was confirmed by peritoneal tap or lavage rather than by computed tomography or abdominal ultrasound. When exsanguination was imminent, the patient was taken directly to the operating theatre without any special investigation. We did not perform emergency thoracotomy for aortic cross-clamping.

Operative mortality refers to all operated patients who died before being discharged, regardless of the cause of death or the length of hospital stay An autopsy was performed in all cases, the results of which were compared with the clinical data to determine the cause of death

Statistical evaluation was accomplished by the χ^2 test (with Yates' correction), the Fisher exact test and the linear trend test when required, calculations were made using the Statistical Package for Social Sciences[25]. Differences were considered significant when *P* values were $\leqslant 0·05$

Results

There were 72 male and 27 female patients with a median age of 30 years (range 16–83 years) admitted during this period. Blunt trauma was the cause of injury in 88 patients; of the remaining 11 hepatic lesions, 7 were due to stabbing and 4 to gunshot wounds. Thirty-seven patients were transferred from outlying hospitals.

Fate of hepatic trauma patients

The majority of patients had widespread trauma, seriously injuring many systems. Only eight patients had trauma confined

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to the liver. The average number of severely injured systems (AIS ≥ 3) was 2·4 for the 88 blunt trauma victims. Most liver wounds were minor (67 patients) and easy to control. In all, 32 patients suffered a major hepatic lesion, 15 of which were treated by resection, including 8 hepatic lobectomies (*Table 1*). There were 35 operative deaths; 14 patients died within a few hours of laparotomy and 21 patients died during the postoperative period. Operative mortality rate was therefore 35 per cent. Blunt trauma and stab wounds carried a 36 per cent (32 of 88 patients) and a 14 per cent (1 of 7 patients) mortality rate respectively. Two of the four patients who had gunshot wounds subsequently died.

Peroperative deaths. The 14 peroperative deaths included 12 in blunt trauma patients, 1 in gunshot patients and 1 after a stab wound. The average number of severely injured systems was 3·8 for blunt trauma victims. Shock on arrival was recorded in ten patients (71 per cent). Isolated complex hepatic injury had occurred in two of those patients. Five further patients who died had a major lesion to the liver in addition to other injuries. Seven patients who died had minor hepatic wounds.

Three patients with a major hepatic injury (plus another one with a minor hepatic lesion) died before the surgeon could complete the laparotomy. Two additional patients with severe hepatic lesions died before adequate surgical treatment of the liver injury could be undertaken because of bleeding from other extra-hepatic sites. The last two patients with serious hepatic damage died in spite of surgical intervention. One presented with such severe liver destruction that the only option left was tamponade using a perihepatic packing. He died of exsanguination during the operation. The other patient died a few hours after right hepatic lobectomy with refractory coagulopathy and persistent bleeding from the hepatic resection margin and from the retroperitoneum.

Altogether, massive bleeding accounted for 12 deaths. Seven deaths were attributed solely to this (two resulted from a massive hepatic bleed); three to haemorrhage and thoracic injury; two to haemorrhage and brain damage. The patient with a minor hepatic wound who died rapidly was an obese man of 79 who developed a fatal arrhythmia secondary to a severe cardiac contusion, hypoxaemia and relative hypovolaemia. The last patient was declared dead by the neurosurgeon at the end of the abdominal operation; autopsy revealed a basal skull fracture with contusion and haematoma of the brain stem.

Postoperative deaths. The 21 postoperative deaths occurred in 20 blunt trauma patients and 1 patient with a gunshot wound. The average number of severely injured systems was 3·1 for blunt trauma victims. Shock was present in 62 per cent of cases (13 of 21 patients).

Major hepatic injury was found in eight patients; in none was this the sole lesion. Surgical management is described in *Table 1*. Four patients underwent a classical hepatic resection. An additional patient had resectional debridement of an extensive lesion due to buckshot; this corresponded approximately to a trisegmentectomy. He died of continuous bleeding with irreversible coagulopathy.

Table 1 *Surgical management of hepatic trauma*

	Survivors	Deaths	Total
Simple hepatic repair and drainage	39	13	52
Mattress suture	7	—	7
Drainage of subcapsular haematoma	1	—	1
Hepatotomy with selective ligation	3	2	5
Perihepatic packing	0	2	2
Hepatic artery ligation	4	1	5
Segmentectomy	6	1	7
Hepatic lobectomy	4	4	8

Twelve patients died intra-operatively before surgical treatment of the liver injury

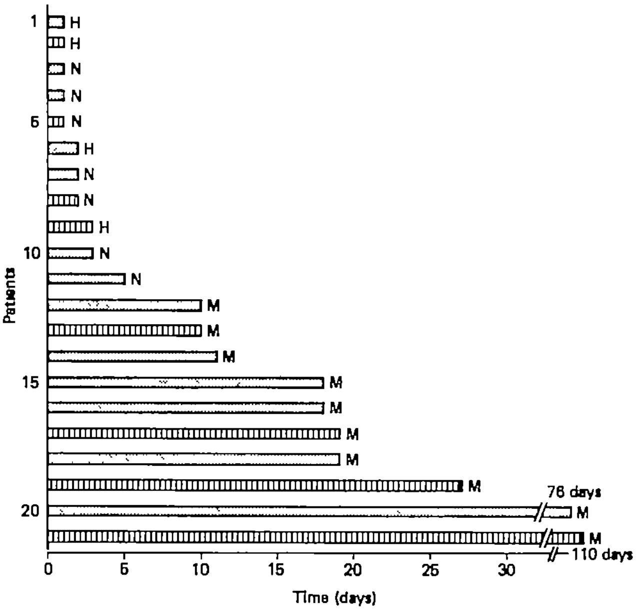

Figure 1 *Cause and timing of the 21 postoperative deaths H, haemorrhage, coagulopathy (4 patients); N, neurosurgical (7 patients), M, 'multiple organ failure' (10 patients);* □, *minor hepatic wounds;* ▥, *major hepatic wounds. The survival time of patients 20 and 21 is given in days*

Patient 21 (*Figure 1*) initially had a right lobar hepatic artery ligation and a right renal embolization; owing to developing sepsis on day 6, she underwent right hepatic lobectomy, to eliminate all necrotic contaminated tissue, and simultaneous removal of her right ischaemic kidney. She died of intra-abdominal sepsis and multiple systemic organ failure after 4 months, in spite of intensive surgical management (including laparostomy) and medical support.

The course and cause of these postoperative deaths is graphically reproduced in *Figure 1*. The early deaths were either due to refractory coagulopathy and persistent bleeding (four patients) or to brain damage (seven patients). Subsequently, sepsis with its classical picture of multiple systemic organ failure accounted for the ten remaining deaths. The origin of sepsis in these polytraumatized, shocked, massively transfused patients appears to have been the lungs in six patients and the abdomen in four patients.

Surviving patients. Of the 64 patients surviving their liver trauma, 56 had suffered blunt trauma, of which the average number of injured systems was 1·9, and 8 penetrating wounds (6 stabbing and 2 gunshot wounds). They presented with a 27 per cent incidence of shock on admission. A major hepatic lesion was encountered in 17 patients, 10 of which were treated by hepatic resection.

Surgical management is listed in *Table 1*. *Table 2* records the major complications that occurred in 45 patients during their stay. It is of interest to note the one patient diagnosed as having a segmental Budd–Chiari syndrome following a bisegmentectomy (segments VII and VIII) with closure of the hepatic section. This patient developed compression of the right major hepatic vein because of an expanding haematoma, the removal of which restored normal blood flow. Another patient presented progressive jaundice after a right hepatic lobectomy, which was corrected by hepatojejunal anastomosis. Although not proven, accidental ligation of the extra-hepatic bile duct was suspected. Two intrahepatic arterioportal vein fistulae were discovered on postoperative arteriography, neither having haemodynamic repercussions. Haemobilia has not been documented.

Factors influencing mortality

Many factors influenced the mortality of our patients presenting with hepatic trauma.

Table 2 *Complications among 64 surviving patients*

Complication	n
External biliary fistula	2
Arterioportal vein fistula	2
Segmental Budd–Chiari syndrome	1
Progressive jaundice	1
Intra-abdominal abscess	4
Gastrointestinal bleeding	3
Gastrointestinal fistula	1
Septicaemia*	14
Small bowel obstruction	2
Lungs (ARDS, pneumonia, etc.)	29
Miscellaneous	10

* Defined as fever and positive blood cultures. ARDS, adult respiratory distress syndrome

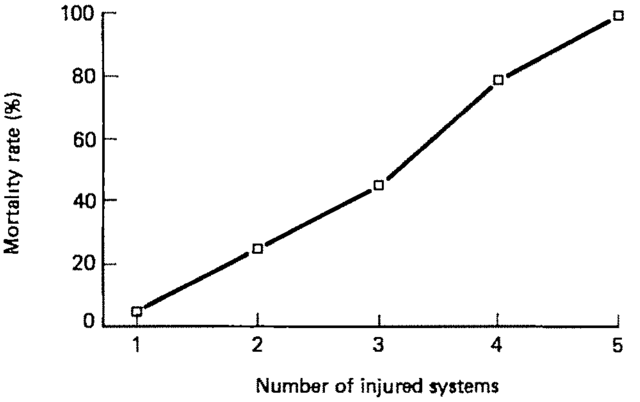

Figure 2 *The relationship between the number of injured systems and the mortality rate*

Associated injuries. Blunt trauma victims (88 patients) showed a steady increase in mortality with each additional system involved. The mortality rate was 5 per cent (1 of 22 patients) when only the abdomen was injured, 25 per cent (7 of 28 patients) with 1 other system involvement, 45 per cent (9 of 20 patients) with 2 other systems, 79 per cent (11 of 14 patients) with 3 other systems, and 100 per cent (4 of 4 patients) when 4 other systems were concurrently injured (*Figure 2*). Statistical analysis, using the linear trend test[25], shows that mortality is significantly related to the number of injured systems.

Considering the abdomen specifically (*Table 3*), an average of 1·0 other intra-abdominal organs were injured in blunt trauma victims in conjunction with their liver wound. The 32 patients who eventually died had an average of 1·4 injuries; whereas for the 56 survivors, this figure was 0·7. The 11 stabbed or shot patients all had their injury confined to the abdomen, the average number of wounded organs, apart from the liver, was 0·7. All three patients who died had an additional visceral lesion: the two stabbed patients were found to have a major vessel laceration (one aorta and one inferior vena cava), the gunshot patient had gastric perforation along with massive destruction of the liver by buckshot.

Certain combinations of liver trauma with other organ lesions were quite ominous: none of the four patients with injury of either the aorta or the vena cava survived. A large retroperitoneal haematoma usually reflects severe damage to the kidney, the spine or the pelvis and was present in five peroperative and in three postoperative deaths. Of the ten patients with intestinal lesions that required resection, three died from sepsis.

Pre-operative shock. The incidence of shock among the dead and the survivors was 66 per cent (23 of 35 deaths) and 27 per cent (17 of 64 survivors), respectively. Of the 40 shocked patients 23 died (10 during urgent laparotomy and 13 during the postoperative period) which gives a combined mortality rate of 58 per cent. The cause of these peroperative deaths was haemorrhage, either alone (five cases) or in conjunction with other critical injuries (five cases); for the postoperative deaths, it was haemorrhage (three cases), sepsis (six cases) and brain damage (four cases). Among the 59 non-shocked patients, 12 ultimately died, including 2 patients operated on immediately because of massive abdominal bleeding, before shock occurred. Haemorrhage was responsible for the fatal outcome in only three patients. Thus, when shock was present the mortality rate was 58 per cent but when absent it was 20 per cent, making pre-operative shock a significant risk factor for death ($P = 0{\cdot}0003$).

Of the 37 transferred patients 19 (51 per cent) had developed pre-operative shock, with 8 ensuing deaths (1 peroperative and 7 postoperative deaths). A total of 12 patients (4 deaths) had correction of hypovolaemia before leaving the outlying hospital, 5 patients (2 deaths) developed shock on arrival at our centre, 2 patients (2 deaths, comprising the sole peroperative death among transferred patients) remained shocked and unresponsive to the resuscitative measures initiated before transferal.

Of the 62 patients who were directly admitted to our medical centre 21 (34 per cent) displayed pre-operative shock, finally leading to 15 deaths (9 peroperative and 6 postoperative deaths). As already stated, two other patients were immediately taken to the operating room before the occurrence of shock. In all, 17 of these 23 profusely bleeding patients could be traced by police department records to give a precise timing of their accident. The transportation time of these patients to our hospital varied from 3 to 25 min, with a median time of 13 min. Altogether, nine patients were expedited for operation within a few minutes after admission; six died, because of haemorrhage (five cases) or subsequent sepsis (one case).

Of the 14 peroperative deaths 13 occurred in patients being sent straight to our centre. This highlights the gravity of the injury they had sustained.

Age. The 16 patients over 50 years had a 63 per cent mortality rate, whereas the 83 younger patients had a 30 per cent death rate ($P = 0{\cdot}028$). The six survivors of the small group of older patients had all injury confined to the abdomen; furthermore, only two of them had injury to another intra-abdominal organ. Some young people were able to survive injury to three (11 of 19 patients) or even four (3 of 10 patients) systems although no-one survived injury to five systems (four deaths).

Nature of trauma. Blunt hepatic trauma led to 32 deaths in 88 patients (36 per cent) and stab wounds to 1 death in 7 patients (14 per cent, $P = 0{\cdot}42$).

Table 3 *Associated intra-abdominal injuries in 99 hepatic trauma patients*

	Blunt trauma ($n = 88$)		Stab and gunshot wounds ($n = 11$)	
Spleen	28	(13)	—	—
Stomach and small bowel	10	(4)	3	(2)
Colon	6	(2)	1	—
Mesentery	9	(5)	1	—
Pancreas	1	(1)	—	—
Diaphragm	6	(3)	—	—
Aorta	1	(1)	1	(1)
Inferior vena cava	1	(1)	1	(1)
Portal or mesenteric vessels	2	(1)	2	(2)
Kidney	10	(4)	—	—
Bladder and urethra	4	(1)	—	—
Adrenals	1	(1)	—	—
Retroperitoneal haematoma*	12	(8)	—	—

Values in parentheses indicate the number of subsequent deaths. * Origin of injury. spine in 4 patients, pelvis in 4 patients, kidney in 3 patients, unclear in 1 patient

Hepatic injury and its treatment. These two parameters cannot be considered separately in a retrospective study[15]. Together they defined a 47 per cent mortality rate (15 of 32 patients) for major injuries and a 30 per cent mortality rate (20 of 67 patients) for more minor lesions. This difference does not reach statistical significance ($P = 0{\cdot}152$). Nevertheless, it should be recalled that six patients succumbed to their liver wound exclusively.

Mortality rates defined by the gravity of the hepatic injury were not influenced by age (17 per cent of patients with a major hepatic lesion and 16 per cent of those with a minor hepatic lesion were over 50 years of age, median ages being 32 and 30 years, respectively). The impact of the other risk factors is more difficult to determine, partly because of the diversity of injuries in blunt trauma and partly because of the complex inter-relationships between parameters used in assessing physiological derangements and anatomical disruption. The average number of systems injured was identical in both groups; it was 2·3 for patients with major and 2·1 for patients with minor hepatic wounds. However, neurologically related deaths were more prevalent in patients who had a minor lesion to the liver (five cases) than in those with a major one (two cases). On the other hand, shock—an expression of profound physiological upset and thus a highly reliable prognostic indicator—was recorded more frequently in patients with major hepatic damage (54 per cent of cases) than in those with only minor injury (30 per cent of cases).

Resection itself carried a 33 per cent mortality rate with a 50 per cent mortality rate for hepatic lobectomy (4 of 8 patients). Bleeding had stopped in all five patients with hepatic artery ligation, yet one developed an infected hepatic haematoma and subsequently died, following hepatic lobectomy, performed a few days later; another patient died of brain damage. Packing was resorted to only twice. Both patients died, the first one peroperatively and the second one, referred by another hospital where he was operated on, died the next day of brain damage without reoperation.

Discussion

Hepatic injury carries a high mortality rate, with shotgun and blunt trauma being the most lethal[4,18,21,26]. Many factors contributed to our 35 per cent operative mortality rate. It is a reflection of the high proportion of blunt trauma patients dealt with and a consequence of the transfer of many seriously injured patients to our reference centre from peripheral hospitals. Furthermore, Geneva's urban area, with its centrally located University Hospital, is exceptional in that the transportation time from the scene of an accident to the hospital usually does not exceed 15 min. In 1984, a prospective study in our city evaluated the efficiency of prehospital care delivered to cardiac emergencies[27]. The median time required by ambulances for patient transportation was 5·2 min; 85 per cent of the patients were admitted within 8 min. Cardiac emergencies undoubtedly are more frequent in the populated downtown area than at the city's periphery where most traffic accidents occur. The present retrospective analysis confirms the remarkable rapidity with which our hospital can be reached (median transportation time 13 min). Resuscitative measures were undertaken at the scene of the accident by a trained team which would initiate crystalloid infusion and perform endotracheal intubation when necessary. For many years, we have been experiencing the paradox of efficient prehospital handling[18] which, while improving the absolute salvage rate, has caused an increase in hospital mortality.

It is difficult to attribute the cause of death to a specific system when considering multiple trauma patients. Many fatalities were unrelated to the hepatic damage, as is demonstrated by the 20 deaths reported among patients with minor hepatic wounds. On the other hand, six deaths were directly due to liver injury: namely the five patients who died of uncontrolled bleeding and the one patient who died with intra-abdominal sepsis. The hepatic involvement played a role in the fatal outcome in the remaining nine patients in conjunction with serious injury to other organs.

Factors which definitely worsened the prognosis were multiple trauma, pre-operative shock, and age over 50 years. Blunt trauma to the abdomen and major hepatic injury with its surgical treatment had less influence on the outcome—even if 6 patients died because of the liver injury itself. As shown in *Figure 2*, the mortality rate increased significantly with each additional system that was seriously injured.

Comparison of different studies concerning conservative and resectional surgical management of liver trauma is impossible as long as no standard severity index of hepatic injury exists. During these 10 years, we have resorted liberally to resection (15 per cent of patients) when faced with an extensive hepatic lesion. We certainly have not fully utilized the potential offered by hepatotomy with direct ligation of damaged vessels and biliary ducts[24,28]. This technique provides both effective haemostatis and economical sacrifice of hepatic tissue. These two achievements become critical for patients with risk factors such as shock, widespread trauma or blunt hepatic injury. In these settings, the observed liver wound underestimates the magnitude of the hepatic lesion. Remote hepatocytes certainly suffer from temporary dysfunction due to the energy they have absorbed during blunt trauma. The super-imposed shock, hepatic venous stasis and/or hypoxaemia (following thoracic injury or subsequent adult respiratory distress syndrome) will constitute additional insults to the liver parenchyma[29–31]. Teams familiar with the hepatotomy technique report neither rebleeding problems nor excessive infectious or biliary complications[15,24,28]. Their results and the rationale for this technique should promote it as a procedure of choice for the surgical approach to most major hepatic wounds.

The excessive mortality of lobar hepatic resection reported by our series and other studies[22,23,33–35] prohibits its liberal use in hepatic trauma. The exceptional patient with bursting of an entire hepatic lobe remains probably the sole candidate for such radical treatment.

A small well defined subset of patients will also benefit from temporary perihepatic packing. The main indications are to tamponade non-mechanical bleeding arising from a progressing coagulopathy and to allow transfer of the patient to a specialized centre[36–40]. The correct timing for reoperation prevents any increase in infectious complications and provides the best conditions for definitive surgical treatment[41,42].

Among the different options offered to achieve haemostasis, the place of hepatic artery ligation remains uncertain and highly disputed[22,24,43]. All five patients we treated in this way stopped bleeding. However, one subsequently developed infection of the liver haematoma and the surrounding necrotic tissues. Perhaps, hepatic artery ligation should ultimately follow failure of the direct vascular control, provided that arterial clamping at the hilus has clearly demonstrated its effectiveness.

Management of perihepatic vein disruption (retrohepatic vena cava and major hepatic veins) is still controversial[9,18,44]. Prompt vascular isolation of the liver remains a formidable technical problem[4,10] It is presently unclear whether the growing number of hepatic transplantation centres will aid the exsanguinating patient by providing expertise in total vascular exclusion. Access to the wounded vein should then probably be achieved through hepatotomy rather than through hepatic lobectomy[33].

Our approach to major hepatic injury has evolved in the light of the present results. Rapid control of hepatic bleeding (which directly caused five of our deaths) is the surgeon's greatest challenge. This is best achieved with optimal exposure and a well organized plan of management. We favour a generous right transverse incision extending from just above the navel, joining a classical midline incision. This provides a wide view and permits hepatic mobilization. When lacerations bleed profusely, the portal triad is occluded before the liver lesion is directly tackled. The finger fracture hepatotomy is now our preferred treatment. Autotransfusion is reserved for massive haemorrhage, after intestinal contamination has been ruled out. The possibility of perihepatic packing is kept in mind at all times. It is indicated either as an initial measure to minimize the liver blood loss while improving haemodynamic stability and controlling other remote bleeding sources, or as a more definitive measure, at the earliest sign of ensuing severe coagulopathy. The above principles should result in major hepatic resection becoming exceptional and probably will make hepatic artery ligation an even more infrequently used procedure.

Prevention of infection (the second commonest cause of hepatic related deaths) is essentially the same in our new approach to liver trauma as it was previously. It depends on a thorough debridement of devitalized tissue, on a careful search for biliary leaks and on efficient dependent drainage. Antibiotic prophylaxis remains tailored to each individual case.

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Tumour calcification following repeated hepatic de-arterialization in patients: a preliminary communication

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A novel method of repeated hepatic de-arterialization is presented. A vascular occluder is placed around the hepatic artery and connected to an injection port. The hepatic artery can thereafter be occluded repeatedly. Patients with irresectable liver metastases from colorectal cancers were treated with occlusions of the hepatic artery for 1 h twice daily, in combination with intraperitoneal cyclic administration of 5-fluorouracil. The first three patients treated are presented. They all exhibited massive tumour calcifications in the liver reflecting tumour necrosis and resorption. This therapeutic principle must undergo further clinical trials.

Keywords: Liver tumour, de-arterialization, hepatic artery, tumour calcification

It is now 20 years since the first results of using hepatic artery ligation in the treatment of human liver tumour were reported[1,2]. The first report from our own group contained details of impressive tumour regression allowing, in some cases, subsequent resection of previously irresectable tumours. This early favourable result, however, has not been borne out in subsequent clinical trials[3-5]. Many modifications of hepatic arterial obstruction have been attempted but results have been poor with the exception of their use in hepatic carcinoid tumours[6].

We have today a better understanding of the mechanisms of the tumoricidal cytotoxic effects of obstructing the arterial blood supply to liver tumours. Occlusion for 60 min does not induce formation of arterial collaterals[7]. Cytotoxic oxygen free radicals are generated within 15 min of occlusion[8]. Therefore we have been trying to treat patients with occlusion of hepatic artery twice daily for 45–60 min. The patient is treated as long as he lives. The treatment is performed on an ambulatory basis. For this purpose we have developed a special vascular occluder.

The vascular occluder consists of a silicone balloon which is attached to sleeves. The sleeves are sewn around the hepatic artery and the balloon is connected via a small catheter to a subcutaneous injection port (*Figure 1*). By injecting a few millilitres of saline the balloon is inflated and the artery compressed within the ring. The occlusion can be performed by the patient himself. For further review, see Bengmark *et al.*[9].

We report the first three cases treated with this modality. Tumour calcification has occurred in all three patients in parallel with other signs of tumour regression. Tumour calcification in liver tumours is rarely seen spontaneously or after treatment. It is generally believed that calcification develops after the appearance of necrosis and constitutes a good prognostic sign.

Case reports

Case 1

This 53-year-old woman had liver metastases from a rectal cancer. Approximately 75 per cent of the liver volume was involved with tumour. The liver was enlarged reaching down to the iliac crest. The patient was operated on in late June 1985 with implantation of an occluder around the hepatic artery and a catheter for intraperitoneal infusion of cytotoxic drugs. She was treated for 10 months with intermittent occlusion of the hepatic artery combined with intraperitoneal infusion of 5-fluorouracil (5-FU). The hepatic artery was occluded for 1 h twice daily. In addition, 5-FU was administered intraperitoneally in a dose of 1000 mg daily for 1 week every 6 weeks. She had a total of six courses. During the last three courses the 5-FU was omitted because of the appearance of ascites. On CT examination 3 months after start of therapy, tumour regression could be observed with massive calcification. The liver size was reduced and the liver edge was palpable under the costal margin. The calcification increased during the treatment. The patient died 13 months after start of treatment owing to progression of extrahepatic tumour growth.

Case 2

This 50-year-old man had liver metastases from a colonic cancer. At the time of operation the tumour involvement of the liver was estimated to 20 per cent with tumour growth in both lobes. The patient underwent daily occlusions of the hepatic artery for three periods of 1 h. He was only hospitalized for 5 days every 6 weeks when he had intraperitoneal infusion of 5-FU (1000 mg). Five months after start of treatment, marked

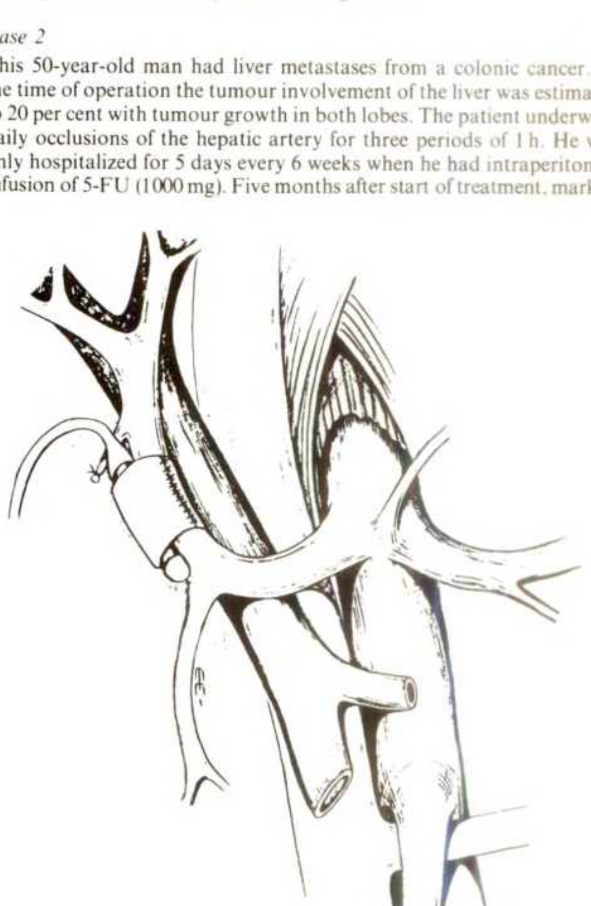

Figure 1 *Model for repeated hepatic de-arterialization. The balloon is connected to a subcutaneous injection port. The artery is compressed within the cuff when the balloon is inflated.*

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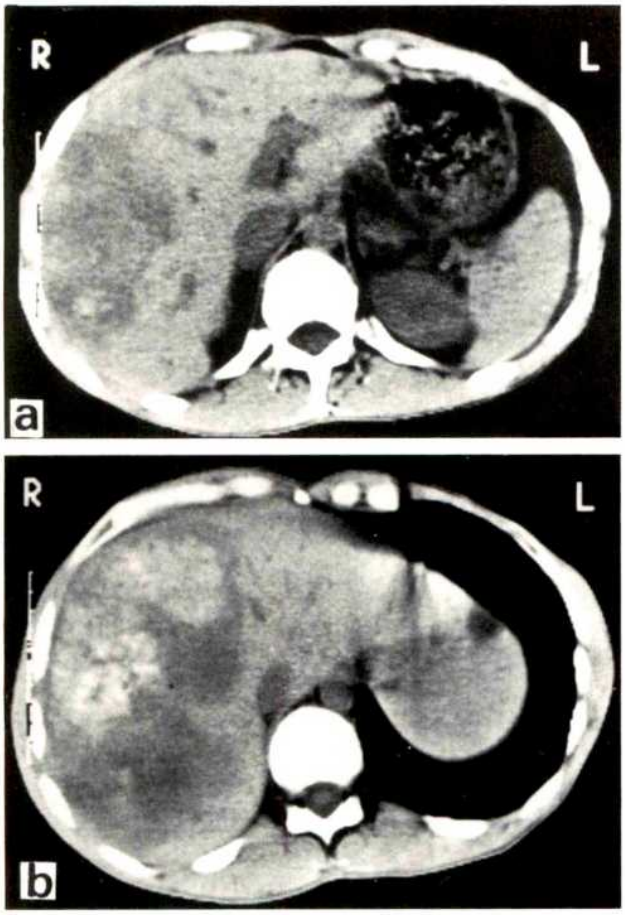

Figure 2 *Case 3. CT scan* **a** *before start of treatment and* **b** *5 months later with tumour calcifications*

tumour regression could be seen on CT. Liver tumour calcification appeared simultaneously. The patient is still alive and working 18 months after start of therapy.

Case 3 (Figure 2)

This 40-year-old man had liver metastases from a rectal cancer. Tumour involvement of the liver was estimated to 50 per cent at laparotomy. The patient was operated on with implantation of an occluder around the hepatic artery and an intraperitoneal infusional device. He then underwent treatment as above with occlusion of the hepatic artery for two periods of 45 min every day. He also had five courses of intraperitoneal infusion of 1000 mg 5-FU over 5 days at 6 week intervals. He has only been hospitalized during the intraperitoneal infusions. Five months after start of treatment, calcification appeared in the tumours and the liver was reduced in size as evaluated by CT scan. The calcification increased during treatment. The patient is still alive 22 months after initiation of therapy and is doing well at home.

All three patients performed the occlusions themselves. They experienced a dull pain in the right upper quadrant at the end of the occlusion. The pain disappeared rapidly after release of the occlusion. At the first occlusion serum levels of transaminases were analysed and there was a small increase (30–60 per cent) in all patients 60 min after release of the occlusion.

Discussion

Hepatic tumour calcifications are rarely seen, even with the aid of modern diagnostic tools like CT scanning and ultrasonography. It is generally believed that tumour calcification indicates tissue destruction and develops after spontaneous or treatment-induced necrosis. Few reports appear in the literature describing tumour calcification following successful therapy. The constant development of tumour calcification in parallel to other signs of tumour regression has made us believe that the tumour calcification is induced by treatment with repeated hepatic ischaemia. It should be noted that in addition to the repeated ischaemia these patients have received infusion of 5-FU for 5 days every 6 weeks. In a case of hepatic metastases from pseudomyxoma peritonei treated with intraperitoneal 5-FU, tumour calcifications appeared concomitantly with a fall in carcino-embryonic antigen[10]. Except for this, 5-FU administration has never been found to lead to tumour calcification in the liver. It cannot be excluded, however, that the tumour calcification is a result of the combined treatment with hepatic ischaemia and intraperitoneal 5-FU infusion.

These first results of repeated transient occlusion of the hepatic artery are promising and this therapeutic principle must undergo further clinical trials.

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Pulmonary complications after subtotal oesophagectomy

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The postoperative pulmonary complications in 25 patients undergoing subtotal oesophagectomy for intrathoracic oesophageal carcinoma during the 3-year period 1981–1983 were compared with those of 25 patients undergoing surgery from 1984 to 1986. Although more extensive lymphadenectomies were performed from 1984, the mortality rate caused by the postoperative pulmonary complications was zero in the later period (1984–1986) compared with a rate of 16 per cent in the earlier period (1981–1983). The incidence of postoperative pulmonary complications was lower in the later series but the difference was not statistically significant. Factors which may have contributed to the decrease in critical pulmonary complications after surgery during the later period were the selection of the posterior mediastinal route for reconstruction, the introduction of selective endobronchial intubation by a double lumen tube with combined epidural anaesthesia, fluid restriction during and after surgery, postoperative mobilization and the administration of an expectorant.

Keywords: Oesophageal carcinoma, pulmonary complications, mechanical ventilation, surgery

In recent years, operations for oesophageal carcinoma have become more radical and more extensive, but oesophagectomy is still associated with a high rate of postoperative complications, especially pulmonary complications and anastomotic leakage. The frequency of anastomotic leaks has decreased appreciably, but pulmonary and cardiac complications remain a problem[1]. The postoperative mortality rate has decreased, from approximately 40 per cent in the reports from the 1940s to a currently quoted rate of 15 per cent. More recently further improvement is reported[2–6], but many unresolved problems remain. To avoid postoperative lung complications, Orringer[7] recommended blunt transhiatal oesophagectomy without thoracotomy. He reported that the survival rates for patients undergoing blunt dissection without thoracotomy are similar to those reported in many series of standard transthoracic oesophagectomies for carcinoma. However, the transhiatal approach in patients with oesophageal carcinoma remains controversial, especially regarding curative surgery. In our clinic, alterations in anaesthetic and operative techniques and postoperative care during the past 3 years have led to an appreciably reduced frequency of postoperative pulmonary complications.

This study was designed to analyse the factors contributing to the decreased mortality from pulmonary complications in patients undergoing subtotal oesophagectomy for intrathoracic carcinomas by comparing two periods: 1981–1983; and 1984–1986.

Patients and methods

Fifty patients undergoing radical one-stage oesophagectomy were divided into two groups: the first group consisted of 25 patients treated from 1981–1983, and the second group consisted of 25 patients treated between 1984 and 1986 All the patients underwent total resection of the oesophagus through a right thoracotomy and abdominal approach, followed by reconstruction with a gastric tube as an oesophageal substitute via a retrosternal route (1981–1983) or via a posterior mediastinal route (1984–1986). The oesophagogastric anastomosis was constructed manually in the neck.

In the earlier group, there were 15 men and 10 women, whose ages ranged from 52 to 68 years, with an average age of 61·5 years In the later group, the ages ranged from 53 to 67 years (mean 60 3 years), with a male:female ratio of 13 12. Tumour stages according to TNM classification[8] were comparable between the two groups The earlier group was constituted as follows. stage I, 3 cases, stage II, 4 cases, stage III, 17 cases, stage IV, one case. The later group consisted of stage I, 4, stage II, 5; stage III, 15, and stage IV, 1 All tumours in the two groups were squamous cell carcinomas and tumour locations were also comparable. In the later group a formal attempt was made to conduct a more radical and more extended lymphadenectomy We made every effort to dissect the lymph nodes in the upper mediastinum, especially the peritracheal lymph nodes and those along the brachiocephalic and jugular vessels, preserving the bronchial branches of vagal nerve and the tracheobronchial arteries Furthermore, the deep cervical and supraclavicular lymph nodes were resected by partial bilateral neck dissection from 1984 onwards.

Nutritional support for oesophageal cancer patients in this series consisted of pre-operative and postoperative total parenteral nutrition providing 40 kcal kg^{-1} day^{-1} which contained 1 5–2·0 g kg^{-1} of amino acids and 1·0–2·0 g kg^{-1} of lipid emulsion, and a non-protein calorie. nitrogen ratio of between 150 and 200.

Intra-operative and postoperative care changed in the following ways between the two periods: in the later period, we introduced selective endobronchial intubation using a double lumen tube[9] with additional epidural anaesthesia. Separate ventilation of each lung was performed with the aid of two gravimetric respirators. In the case of right thoracotomy, the left lung was ventilated with a mixture of O_2 and N_2O and the right lung with an O_2–air mixture Postoperative assisted ventilation was avoided or used for as short a time as possible Before weaning from postoperative mechanical ventilation the following conditions had to be fulfilled: $P_{a,O_2} > 80$ mmHg and $P_{a,CO_2} < 40$ mmHg at inspired oxygen content <40 per cent and strength of expectoration which was judged adequate.

The amount of fluid and sodium administered during and after surgery was restricted in the later patients The amount of intra-operative intravenous fluid given was >10 ml kg^{-1} h^{-1} in the earlier group, but only 5–6 ml kg^{-1} h^{-1} in the later group Moreover, the amount of sodium administered in the former and the latter period was $1{\cdot}2 \pm 0{\cdot}3$ mmol kg^{-1} h^{-1} and $0{\cdot}8 \pm 0{\cdot}2$ mmol kg^{-1} h^{-1} respectively. The patients were mobilized as early as possible after surgery and an expectorant was given.

Pulmonary function tests and blood gas analyses were performed by standard methods. Plasma renin and aldosterone concentrations were measured by radioimmunoassay[10,11] Lung compliance was determined on an ERICA monitor (Engstrom, Sweden). The diagnosis of pulmonary complications was made on the basis of clinical and radiological findings. Pulmonary complications were categorized with respect to location (right or left), and type (atelectasis, pulmonary oedema, bronchopneumonia and other pulmonary abnormalities). The osmolarity of urine was measured by an osmometer and urinary sodium

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Table 1 *Comparison of pre-operative pulmonary function tests by spirogram between the two groups*

	Forced vital capacity (litres)	% Forced vital capacity†	% Forced expiratory volume at 1 s	Maximal mid-expiratory flow rate (litres/s)
Earlier group	2·93±0·97	95·2±18·8	75·6±11·1	2·24±1·23
(−)	3·09±1·04	97·2±15·4	74·4±13·0	2·21±1·53
(+)	2·77±0·95	96·8±17·8	76·4±10·7	2·43±1·02
Later group	3·36±1·01	108·4±18·0*	79·9±10·6	2·65±1·14
(−)	3·46±1·04	109·3±18·2	79·0±11·0	2·64±1·24
(+)	3·09±0·79	105·0±16·7	83·2±6·1	2·70±0·25

*Significantly different from the earlier group ($P<0·05$), †ratio of measured forced vital capacity: predicted forced vital capacity; +, patients with postoperative pulmonary complications; −, patients without postoperative pulmonary complications

Table 2 *Changes in pulmonary compliance influenced by operative posture*

	Pulmonary compliance (ml cmH_2O^{-1})		
	Supine position	Left lateral decubitus position	Difference by operative posture (%)
Right lung (upward)	40·2±11·9	38·9±11·8	−3
Left lung (downward)	34·7±8·6	30·4±11·1	−12

Values are mean±s.d.

and potassium excretion were also checked during surgery and the postoperative period.

Statistical analysis was carried out using Student's *t* test and χ^2 test

Results

Postoperative pulmonary complications and mortality rate

Of the 25 oesophagectomies for intrathoracic oesophageal carcinomas carried out from 1981–1983, pulmonary complications developed in 8 cases, whereas only 4 of 25 cases developed pulmonary problems between 1984 and 1986. The pulmonary complications during the earlier period resulted in four deaths, a mortality rate of 16 per cent, whereas there were no deaths during the later period; this difference was statistically significant by χ^2 test ($P<0·05$). Two clinical anastomotic leaks occurred in the earlier group, whereas there were no leaks in the later period. These data suggest that the reconstruction performed through the posterior mediastinal route might be superior to that using the retrosternal route.

Relationship between pre-operative pulmonary function and blood gas analysis and postoperative pulmonary complications

There were no significant differences with respect to age and sex distribution between the two groups. In the pre-operative pulmonary function tests, there was a significant difference between the two series in relation to the ratio of measured forced vital capacity: predicted forced vital capacity ($P<0·05$), whereas there were no significant differences with regard to forced vital capacity, the percentage of forced expiratory volume at 1 s and maximal midexpiratory flow rate. In each chronological period, there were no significant differences between patients with and without postoperative complications regarding pre-operative pulmonary function (*Table 1*). In the blood gas analysis before surgery, there were no significant differences between the two chronological periods, but there were significant differences in the later group between patients with and without pulmonary complications with respect to the pre-operative P_{a,O_2} ($P<0·01$).

Intra-operative respiratory care and relationship between the duration of assisted ventilation and pulmonary complications

A comparison of the changes in compliance in each lung by operative posture is indicated in *Table 2*. The compliance of the left lung in the left lateral decubitus position was reduced by blood redistribution due to gravity as compared with compliance in the supine position. The inspired oxygen content (F_IO_2) required to maintain the same level of arterial oxygen tension was significantly lower in patients intubated with a double lumen tube than in those intubated with a single lumen tube ($P<0·001$) (*Table 3*). *Table 4* shows a comparison of the two groups regarding the time spent on the ventilator after surgery. The difference between the two groups was highly significant ($P<0·001$).

Postoperative water and electrolytes metabolism

There was a significant difference between the two groups regarding the amount of salt and water administered intra-operatively ($P<0·001$) (*Table 5*). The mean volume of fluid given postoperatively was $>50\,ml\,kg^{-1}\,h^{-1}$ for the first group, but only $40\,ml\,kg^{-1}\,h^{-1}$ for the second group; the difference between the two groups was significant (*Figure 1*). The postoperative urine output in the earlier series reached peak levels on the second postoperative day and decreased thereafter, whereas the output in the later series peaked on the first

Table 3 *Changes in pulmonary arterial oxygen tension with selective endobronchial intubation compared with ordinary intubation*

	P_{a,O_2} (mmHg)			
Intubating tube	Supine position	Left lateral decubitus position	Difference by operative posture (%)	F_IO_2
Single lumen ($n=7$)	170±21	142±27†	−16	0·45±0·08*
Double lumen ($n=10$)	156±30	139±21	−11	0·34±0·03

Values given are mean±s.d. * Significantly different from double lumen tube ($P<0·001$), † no significant difference between single and double lumen tube; F_IO_2, inspired oxygen content

Table 4 *Comparison between the two series with respect to the duration of assisted ventilation following surgery*

Chronological periods	No. of patients*	Duration of assisted ventilation (days)
1981–1983	21	2·8±1·3 †
1984–1986	25	1·2±0·4

* The patients who required long-term respiratory support for respiratory failure were excluded, † the two groups were significantly different ($P<0·001$)

Table 5 *Differences in the amounts of water and sodium administered during surgery during the two periods*

Chronological periods	No. of patients	Water (ml kg^{-1} h^{-1})	Sodium (mmol kg^{-1} h^{-1})
1981–1983	25	10·9±3.3 *	1·2±0·3 *
1984–1986	25	5·8±0·9	0·8±0·2

* Significant difference between the two groups ($P<0·001$)

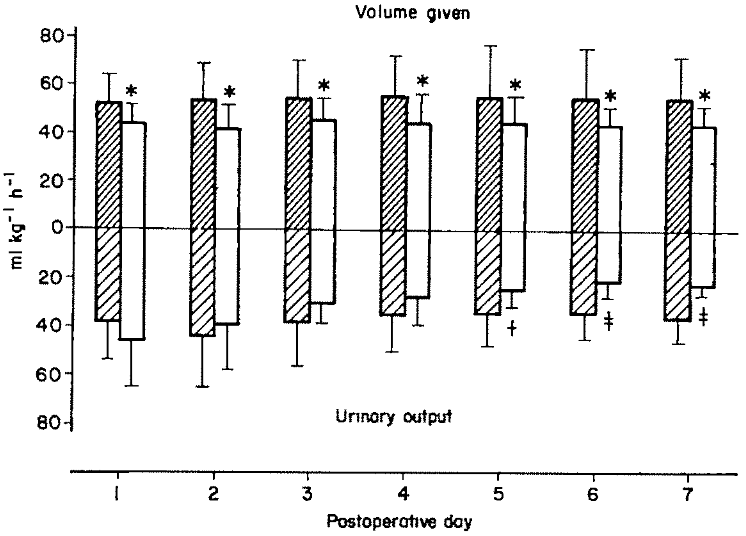

Figure 1 Comparison between the two series of patients regarding the amounts of fluid replacement and urinary output after oesophagectomy ▨, 1981–1983; □, 1984–1986, * significant difference between the two groups ($P<0{\cdot}05$), † $P<0{\cdot}01$; ‡ $P<0{\cdot}001$

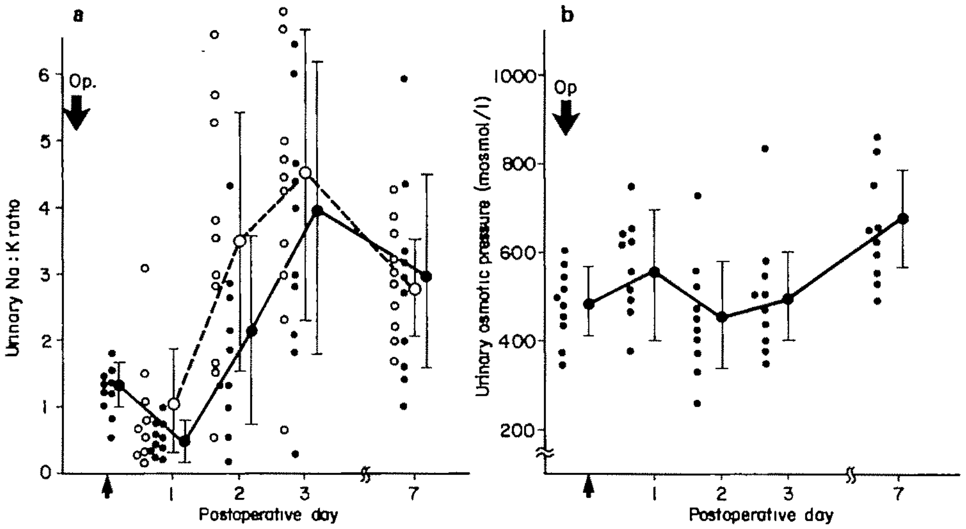

Figure 2 Changes in the urinary Na:K ratio in both groups and the urinary osmotic pressure in the second group; a, Na:K ratio; b, urinary osmolarity, ○, 1981–1983, ●, 1984–1986

postoperative day and then decreased only slightly. *Figure 2* illustrates the change in the urinary Na:K ratio and osmolarity after oesophagectomy in the two groups. The urinary Na:K ratio changed in a similar fashion in both groups. In general, postoperative pulmonary complications tended to develop in patients with decreased sodium excretion and increased potassium excretion in urine, consequently prolonged lower values of urinary Na:K ratio after surgery. It is noteworthy that the postoperative changes in urinary Na:K ratio in the later series were less marked due to significantly lower sodium administrations (*Table 5*) than those in the earlier group.

Postoperative fluctuations of plasma renin and aldosterone

The postoperative changes in the plasma renin and aldosterone stabilized on the second postoperative day and remained stable thereafter. There was no significant correlation between the levels of these hormones and the urinary output or the Na:K ratio.

Discussion

Despite improvements in operative technique and perioperative care, oesophageal resection and reconstruction in patients with cancer remains a formidable operation[12,13] In order to improve the surgical results for cancer of the oesophagus, it is important to analyse the reasons for surgical failure.

Oesophagectomy through a thoraco-abdominal approach for intrathoracic carcinomas is still associated with a high rate of complications, mainly in the form of anastomotic leakage[14] and pulmonary complications[15]. The present analysis represents an effort to detect the reasons for postoperative pulmonary complications. It must be stressed that this is not a controlled randomized study, but a retrospective analysis of two chronologically different groups of patients who had different types of reconstructions, different grades of lymphadenectomy and differing perioperative care. However, the operations were all performed by the same team and all of the patients had squamous cell carcinomas.

Factors liable to induce respiratory insufficiency include advanced age, smoking, obesity, chronic lung diseases, hypofunction of the lung, aggressive lymphadenectomy and inadequate respiratory or infusion therapy during and after oesophagectomy. Our results show that serious lung complications are not inevitable even in patients undergoing extensive lymphadenectomy, despite our anxiety that the posterior mediastinal route might cause ill effects such as pulmonary compression in the second group.

Postoperative respiratory care with frequent suction of intrabronchial secretions[16] is mandatory after extended lymphadenectomy which in our second group of patients included the peritracheal, superior mediastinal, and also the cervical lymph nodes. There were fewer lung complications in the later group than in the earlier group. The following factors can be enumerated as a cause for this decrease in pulmonary complications. A significant correlation between pre-operative pulmonary function and the incidence of postoperative respiratory failure has been reported[17]. Although we did not operate on patients with seriously disordered lung function, in our later group there was a significant relationship between pre-operative P_{a,O_2} and the incidence of pulmonary complication.

Individual lung ventilation using a double lumen tube[9], a technique adopted in the later period (1984–1986), appeared to be very helpful. The good results obtained through isolated ventilation were probably due to the improved lung compliance as well as to the prevention of damage to the parenchymal cells from long-term exposure to high levels of oxygen. Isolated ventilation made it possible to maintain an adequate arterial oxygen level with a relatively low inspired oxygen concentration.

In general, the main causes of postoperative hypoxaemia are an imbalance in the distribution of ventilated blood and the increased shunting which results from diffuse atelectasis. Postoperative hypoxaemia may be exacerbated by any additional lung oedema which results from lowering of the osmolarity, increased airway secretions, impaired expectoration, and infection[18–20]. Wound healing is delayed when the patient is hypoxaemic and the development of anastomotic leaks is favoured by hypoxaemia. As postoperative pain induces tachycardia and impairs oxygenation, the later series of patients were anaesthesized with general anaesthesia combined with epidural anaesthesia during surgery. In addition they had epidural infusion of morphine at the end of surgery for postoperative analgesia.

Extended lymphadenectomy can decrease the expectoration of bronchial secretions because of the impairment of the cough reflex resulting from injury to the bronchial branch of the vagus nerve. Decreased function of the respiratory muscles resulting from thoracotomy and stromal oedema of the lung resulting from interference with lymph flow[21] after extensive lymphadenectomy are also risk factors for pulmonary complications. Therefore, patients undergoing extensive lymphadenectomy need both ventilatory support until recovery of the cough reflex and frequent suctioning of the intrabronchial secretions through a fibrescope.

Excess fluid administration during oesophagectomy causes lung oedema. However, as the urinary concentrating function is reduced in elderly patients, extreme fluid restriction in elderly patients is inappropriate. Therefore, the decision regarding the adequacy of volume for the infusion has to be made on the basis of clinical data, such as urinary volume, osmolarity, electrolyte content and central venous pressure. In the later series we attempted to minimize the amount of fluid infused but also gave parenteral nutritional supplementation; no untoward effects on water balance were experienced. Ando *et al.*[22] have also recommended fluid restriction during the early postoperative days.

The fact that no anastomotic leaks developed and that the incidence of pulmonary complications after surgery decreased in the later series suggests that there may be advantages in the posterior mediastinal route for oesophagectomy Further studies into this problem are necessary, especially in elderly patients with chronic obstructive lung diseases.

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Carcinogenic potential of the non-cancerous epithelium in patients with oesophageal cancer

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Detailed histopathological examination of serial blocks and subserial sections of the entire resected oesophagus in 63 patients operated upon for oesophageal cancer revealed 11 associated minute superficial cancers, independent and apart from the main tumours, in 10 patients (15·9 per cent). Only one of these eleven lesions was diagnosed pre-operatively, and only three of the eleven lesions were detected macroscopically on the resected specimens. The high incidence of such coexisting independent lesions may indicate a possible increased multicentric carcinogenic potential in the non-cancerous epithelium of patients who have had an antecedent oesophageal cancer. These results emphasize the need for careful attention to the choice of margins during surgical resection of the oesophagus.

Keywords: Oesophageal cancer, associated superficial cancer

The presence of intra-epithelial carcinoma concomitant with oesophageal cancer[1–3], and the presence of multiple primary[4,5] or intramural skip metastatic lesions[6] in addition to the main tumour are well recognized as specific features of invasive oesophageal cancer. In the surgical treatment of oesophageal cancer, an effort should be made to detect these associated malignant lesions pre-operatively and the surgeon must remove all such lesions completely. A detailed histological examination by serial blocks and subserial sections of the entire resected oesophagus revealed a high incidence of associated minute cancers[7] of less than 1·0 cm in their longest dimension (superficial cancer), separated from the main tumour. These findings have important implications both for the evaluation of the completeness of surgery and for an understanding of the pathogenesis of oesophageal cancer. In the current study, we analysed the clinicopathological findings of a group of patients with oesophageal cancer.

Patients and methods

Between 1975 and 1985, 63 Japanese patients with invasive oesophageal squamous cell cancer underwent oesophagectomy in our clinic. Thirty-six patients received pre-operative radiotherapy (2 Gy of ^{60}Co irradiation for 5 successive days per week, up to a total dose of 30–40 Gy). The irradiated field was designed to cover the main oesophageal lesion and an area of 3 cm above and below the tumour. The resected specimen was fixed in 10 per cent formalin, and the entire oesophagus was serially sectioned as blocks 4–5 cm long and 0·4–0·5 cm wide. All blocks were embedded in paraffin, cut into sections 5 μm thick and processed for haematoxylin and eosin (H–E) and Weigert's elastic stains. These serial blocks and subserial sections enabled us to detect the associated minute superficial lesions which were barely identifiable macroscopically on the resected specimen. Clinical and histological findings were evaluated according to the 'Guidelines for the clinical and pathologic studies on carcinoma of the esophagus'[8]. Superficial oesophageal cancer has been defined as a lesion confined to the mucosa or the submucosa[8,9], regardless of the presence or the absence of metastases in the lymph nodes.

Results

In 10 of 63 patients (15·9 per cent), 11 cancerous lesions, independent and apart from main lesions, were detected histologically. These 11 lesions were obviously not submucosal cancer infiltration or intramural lymphatic cancer embolization from main lesions, and they were all primary superficial oesophageal cancer, as described below. All 10 patients were male and their ages ranged from 52 to 77 years (mean 62 years).

The site of the main oesophageal cancer was upper thoracic in three, middle thoracic in two, and lower thoracic oesophagus in five cases. The mean (±s.d.) length of the main tumour was 4·4 ± 2·2 cm (range 2·5–8·5 cm). Histologically, all tumours were squamous cell carcinomas; the depth of cancer invasion extended to the muscularis propria in two cases, and adventitial involvement was present in eight cases. Four of the ten patients had metastases in the lymph nodes.

Table 1 shows the clinicopathological findings of the 11 associated lesions in 10 patients. Macroscopic epithelial abnormality was noted in only three of the eleven lesions on the resected specimen. The location of these lesions was cervical in one, upper thoracic in two, middle thoracic in three and lower thoracic oesophagus in five cases, respectively

Histologically, all the associated lesions were squamous cell carcinoma and all were superficial cancers, the cancer invasion extended to the epithelium in one case, mucosa in nine cases, and submucosa in one. Histologically, the transition between the superficial cancer and the non-cancerous oesophageal epithelium was abrupt at both proximal and distal margins in seven, two had abrupt transitions for the proximal margin only, one had an abrupt transition for the distal margin only, and one had gradual transitions for both the proximal and distal margins. Four superficial lesions showed a gradual transition to moderate dysplasia of the oesophageal epithelium for both proximal and distal, or either proximal or distal, margins.

The mean length of these lesions was 0·5 ± 0·2 cm, all were less than 1·0 cm in length (range 0·3–0·9 cm).

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Table 1 *Clinicopathological findings of associated superficial cancers*

Patient no (age/sex)	Site	Depth of cancer invasion	Length* (cm)	Direction† (distance: cm)‡	Pre-operative: Radiation to main tumour	Pre-operative: Diagnosis of associated lesion
1. 60/M	Middle	Epithelium	0·4	Distal (5·0)	No	No
2. 60/M	Middle	Mucosa	0·9	Proximal (3·2)	Yes	No
3. 62/M	Middle	Mucosa	0·5	Proximal (7·0)	Yes	No
4. 61/M	Lower	Mucosa	0·9	Distal (0·5)	No	No
5. 62/M	Upper	Mucosa	0·5	Proximal (1·5)	No	No
6. 63/M	Lower	Mucosa	0·5	Distal (6·2)	Yes	No
7. 64/M	Lower	Mucosa	0·3	Proximal (1·5)	No	No
	Lower	Mucosa	0·3	Proximal (2·2)		No
8. 52/M	Lower	Mucosa	0·3	Proximal (3·5)	Yes	No
9. 60/M	Cervical	Mucosa	0·3	Proximal (2·6)	No	No
10. 77/M	Upper	Submucosa	0·6	Proximal (3·0)	No	Yes

Cervical, cervical oesophagus; Upper, upper thoracic oesophagus, Middle, middle thoracic oesophagus. * Length measured on each histological specimen; † direction of the associated lesion in relation to the site of the main cancer; ‡ distance between main and associated superficial cancers

Eight lesions were detected on the proximal side of the main tumour and three were on the distal side, with mean separation for all eleven lesions of 3·3 ± 2·0 cm from the main tumour (range 0·5–7·0 cm). Four of ten patients had received pre-operative radiotherapy. The incidence of associated superficial cancer was 11·1 per cent (4/36) for pre-operatively irradiated patients and 22·2 per cent (6/27) for non-irradiated patients. This difference is not statistically significant. A pre-operative diagnosis of an associated lesion was made in only one case (Case No. 10).

Figure 1 compares the distance between the main and associated cancers in relation to the presence or absence of pre-operative radiotherapy. The mean distance (5·0 ± 1·9 cm) in patients who underwent radiotherapy was longer than that (2·3 ± 1·4 cm) in non-irradiated patients.

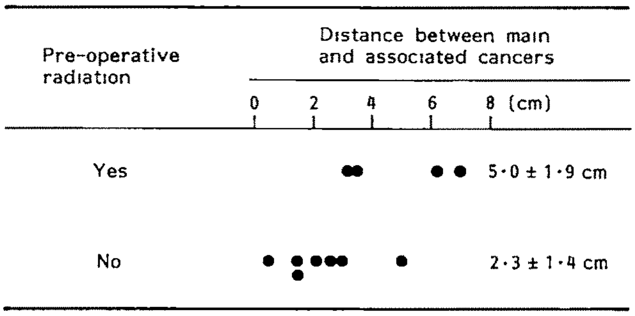

Figure 1 *Distance between main and associated cancers in patients with or without pre-operative radiotherapy. The mean (+s.d.) distance in centimetres is given*

Discussion

In this series, examination of serial blocks and subserial sections of the entire surgically resected specimen gave a rate of 15·9 per cent for the presence of superficial cancer separate from the main tumour. In the surgical treatment of oesophageal cancer, the pre-operative diagnosis of these associated lesions has important implications for the planning of surgery. Although these superficial and minute lesions may be easily overlooked during routine radiographic and endoscopic examinations, endoscopic staining with Lugol's solution has been reported to be useful for the pre-operative detection of such fine superficial epithelial changes of the oesophagus[7,10].

A possible relationship between various degrees of epithelial dysplasia and carcinoma has been suggested[4,9,11]. This is because some intra-epithelial oesophageal carcinomas are frequently surrounded by severe dysplasia and occasionally show a gradual transition to dysplasia, and it seems that dysplasia plays a significant part in carcinogenesis of the oesophagus, as a precursor lesion. In our series, no associated lesion was surrounded by severe dysplasia, although five lesions showed a gradual transition to moderate dysplasia. Although we are unable to elucidate the exact significance of such dysplasia in oesophageal carcinogenesis, the high incidence of these associated lesions may indicate a possible increased multicentric carcinogenic potential in the non-cancerous epithelium of patients who have had an antecedent oesophageal cancer.

In oesophageal surgery, surgeons are required to undertake the complete removal of both the main and associated lesions because of such possible association. Our data indicate a mean distance of 3·3 cm between the main and associated lesions. Given the substantial shrinkage of the oesophageal tissue between the time of operation and fixation in formalin[12], careful attention must be paid to the choice of surgical margins during resection of the oesophagus.

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Gastro-oesophageal reflux and intestinal malrotation in children

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In a series of 74 children undergoing Nissen fundoplication for persistent gastro-oesophageal reflux unresponsive to intensive medical treatment, there was an unexpectedly high incidence (54 per cent, n = *40) of intestinal malrotation. The series was not homogeneous, 25 of the children having reflux as a complication of a serious congenital abnormality (48 per cent incidence of intestinal malrotation), and 49 presenting with 'idiopathic' reflux (57 per cent incidence of intestinal malrotation). Intestinal malrotation is best detected pre-operatively by careful barium radiology, requiring clinicians to be aware of the association. In our experience, in children over the age of 3 months, both an antireflux operation and Ladd's procedure are often necessary to stop gastro-oesophageal reflux when an intestinal malrotation is present.*

Keywords: Gastro-oesophageal reflux, intestinal malrotation, pyloric stenosis, oesophageal atresia, abdominal wall defects

There has been growing appreciation of the extent of gastro-oesophageal reflux in infants and children, and of reflux as a cause of various complications, especially of the respiratory tract. In 1947, Neuhauser and Berenberg[1] described the condition 'chalasia' in 12 infants with relaxation of the cardia as the cause of vomiting. The management was confined to thickening the feeds and attempting to maintain an upright posture. In 1952, Carré *et al.* described hiatus hernia as a cause of unexplained vomiting in children[2] and in 1959, he documented the natural history of 'partial thoracic stomach'[3]. Only in the last decade has it been realized that gastro-oesophageal reflux may be an important cause of failure to thrive, oesophagitis, oesophageal stricture, recurrent pneumonitis, asthma and 'near miss sudden infant death syndrome'[4]. The purpose of our study is to report the poorly documented association of gastro-oesophageal reflux of such severity as to necessitate antireflux surgery with intestinal malrotation.

Patients and methods

During a 4-year period, all infants and children with reflux of such severity as to necessitate antireflux surgery were analysed. The main symptoms of the patients were persistent vomiting, failure to thrive, haematemesis, dysphagia or recurrent respiratory infections which were unresponsive to more conservative forms of management. Patients with 'idiopathic' gastro-oesophageal reflux were included as well as those with reflux associated with congenital anomalies such as intestinal malrotation, oesophageal atresia, diaphragmatic hernia, and exomphalos. Children with reflux associated with neurological diseases were excluded, as our experience in this group has been reported elsewhere[5]. A very large group of patients responding to conservative management either as out-patients, or after a short period in hospital, were excluded. Patients who had intestinal malrotation without demonstrable reflux ($n = 21$) have been excluded from this analysis as they had no antireflux operation.

The principal diagnostic investigation was the upper gastrointestinal barium contrast study, which was performed in all patients. During this examination, the anatomy and peristaltic activity of the oesphagus were assessed. The presence and degree of gastro-oesophageal reflux were noted, as was the ability of the oesophagus to clear the refluxed material. The presence of contrast within the tracheobronchial tree was recorded. The anatomy of the gastric outlet was assessed and the contrast followed through the duodenum into the upper small intestine in order to document the position of the duodenojejunal flexure. This was defined as the first visible kink in the distal part of the duodenum.

Malrotation was diagnosed when there was an abnormal configuration of the duodenal C-loop or when the duodenojejunal flexure was located to the right of the vertebral bodies (*Figure 1*). In doubtful cases, contrast was followed through the small intestine in an attempt to define the position of the caecum. In such cases, malrotation was diagnosed if the caecum was found lying high in the right hypochondrium instead of in the right iliac fossa. Upper gastrointestinal endoscopy was carried out in 69 of the 74 patients. The presence and grade of oesophagitis were noted. The tone of the gastro-oesophageal junction was assessed and the presence or absence of reflux documented. If possible, the stomach, pylorus and proximal duodenum were examined. Technetium-99 sulphur colloid 'milk scans'[6] were performed in six patients. Oesophageal pH and manometric studies were performed in only two patients because the majority had obvious radiological confirmation of severe reflux.

A detailed examination of the position of the caecum, its mesenteric attachments and the site of the duodenojejunal flexure was made in all patients at laparotomy before proceeding to fundoplication. Whenever diagnosed, intestinal malrotation was treated by Ladd's procedure, which consisted of division of Ladd's bands between the duodenum and the caecum and right colon, the gallbladder, and the lateral abdominal

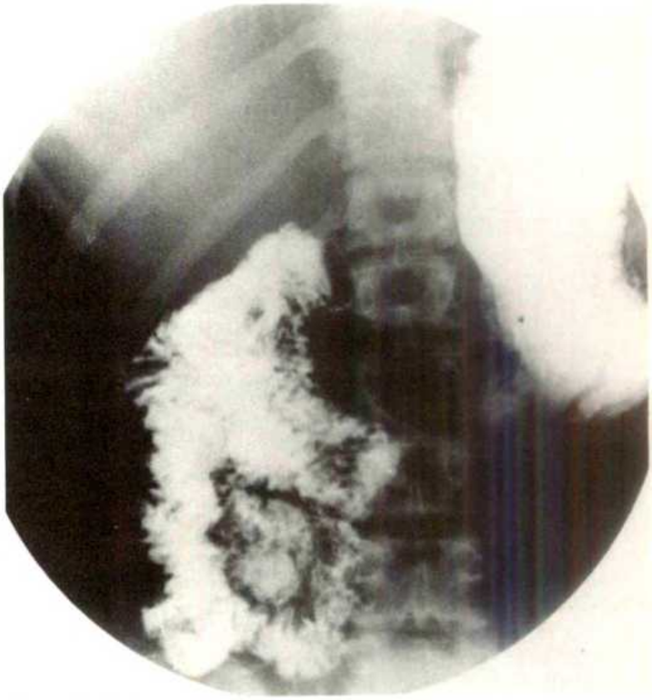

Figure 1 *Radiograph of an upper gastrointestinal contrast study demonstrating midgut malrotation. Note the position of the duodenojejunal flexure to the right of the midline*

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wall. The mobilized colon was placed in the left side of the abdominal cavity with the caecum adjacent to the spleen.

Results

A total of 74 infants and children had reflux demonstrated by barium meal or pH monitoring and subsequently underwent antireflux surgery in the form of a Nissen fundoplication (*Table 1*). The age of the patients at operation ranged from 10 weeks to 13 years (mean age 35·6 months). All patients undergoing surgery during the first year of life had a hiatus hernia. Of the 21 patients undergoing surgery for idiopathic reflux unresponsive to medical treatment, 8 had an established oesophageal stricture. An additional associated congenital anomaly was present in the remaining 53 patients.

Midgut malrotation was found at the barium study, and confirmed at laparotomy, in 32 patients with persistent vomiting. A standard Ladd's procedure was carried out in 18, and a further 14 had a Nissen fundoplication in addition during the same operation because endoscopy performed immediately before surgery had demonstrated marked oesophagitis, confirming the pre-operative radiological findings. All of the latter group were cured of their vomiting but only four infants undergoing Ladd's procedure alone were cured of reflux. Vomiting persisted in 14 of the older children undergoing Ladd's procedure alone and all 14 subsequently required an antireflux operation.

In addition to the 28 patients with isolated malrotation (*Table 1*), 12 children underwent Nissen fundoplication for reflux associated with intestinal malrotation combined with other anomalies, namely pyloric stenosis ($n = 1$), oesophageal atresia ($n = 4$), umbilical defects ($n = 1$) and diaphragmatic hernia ($n = 6$). In 33 patients, the malrotation took the form of a classic incomplete midgut rotation with a narrow-based mesentery and subhepatic caecum. In the remaining seven cases, the malrotation was confined to the duodenum, the duodenojejunal flexure being to the right of the midline, the proximal duodenum being dilated (both on barium meal and at laparotomy) indicating a degree of obstruction. Intrinsic duodenal obstruction was excluded by endoscopy in all of these patients.

In the immediate postoperative period, only one infant developed complications. He presented at the age of 11 weeks with a completely intrathoracic stomach. Postoperatively he developed pneumococcal bronchopneumonia resulting in meningitis and necrotizing enterocolitis. He recovered on medical treatment and, at the age of 16 months, was developing normally. Late complications occurred in seven patients, four of whom developed 'gas bloat syndrome'. The other three developed adhesion obstruction, two of whom recovered after laparotomy. One child died suddenly at home without being referred for medical attention; post-mortem examination revealed gangrenous bowel caused by volvulus about a band adhesion.

Of the 73 survivors, 4 still have mild intermittent gas bloat; 4 children with oesophageal atresia have had a fair result; 12 children were reluctant to feed initially but eventually had a good result, and the antireflux procedure had an immediate and excellent result in the remaining 53 infants and children.

Table 1 *Analysis of 74 patients undergoing Nissen fundoplication for gastrointestinal reflux unresponsive to medical treatment*

Idiopathic GOR	
Without intestinal malrotation	21
With intestinal malrotation	28
GOR associated with serious congenital anomalies	
Midgut malrotation and pyloric stenosis	1
Oesophageal atresia (previous primary repair)	12
Oesophageal atresia and malrotation	4
Oesophageal atresia and pyloric stenosis	1
Exomphalos/gastroschisis and malrotation	1
Diaphragmatic hernia and malrotation	6
Associated malrotation: 40 (54%)	

GOR, gastrointestinal reflux

Discussion

Gastro-oesophageal reflux in infants and children is associated with significant morbidity and with a low, but definite, mortality rate[4]. Only a few reported series have mentioned the association of gastro-oesophageal reflux with congenital anomalies such as intestinal malrotation, pyloric stenosis and oesophageal atresia[7-10]. One-third of our patients were in the group of children with serious congenital abnormalities other than intestinal malrotation, and 17 of these had oesophageal atresia with reflux[11,12]; the remainder of the infants with serious abnormalities had abdominal wall defects including diaphragmatic hernia, exomphalos and gastroschisis with intestinal malrotation as a component of the basic embryological defect. The incidence of intestinal malrotation in infants with oesophageal atresia is unknown, but at least 3 per cent of patients are affected[13]. The role of reflux in pyloric stenosis, and the effect of reflux oesophagitis on the incidence and severity of postoperative vomiting, have been well documented[14].

Most children with gastro-oesophageal reflux do not have obvious associated congenital anomalies and the magnitude of the problem of idiopathic reflux is far greater than that first defined by Carré *et al.*[2]. Bettex and Kuffer[15] published the results of fundoplication for uncomplicated hiatus hernia in 194 children. As we do not have detailed figures for the larger number of infants treated conservatively in our out-patient clinics, or by our medical colleagues, we accept that the patients in this series may not be representative of those presenting in other centres. Many of the patients had been investigated and treated elsewhere before being referred to our surgical unit. Two-thirds of our patients were without apparent congenital abnormality, but 57 per cent of these were found to have midgut malrotation, which has emerged as the most common associated anomaly. This high incidence is all the more surprising because it exceeds that of 48 per cent for the group with other serious congenital anomalies. This is largely attributable to careful attention to the position of the duodenojejunal flexure during the upper gastrointestinal radiological study and at laparotomy before fundoplication. Obviously, the incidence is biased as all children with severe reflux and diagnosed intestinal malrotation underwent operation, whereas numerous children with reflux without a proven malrotation were successfully treated without operation. Similarly, bias may have been introduced by the exclusion of the 21 patients with malrotation in whom reflux could not be demonstrated. However, we are concerned only with the incidence of intestinal malrotation in those with reflux of such severity as to necessitate an antireflux operation.

Intestinal malrotation may be easily overlooked on the barium meal. Before presenting here with persistent vomiting and failure to thrive, two patients had undergone unsuccessful antireflux procedures elsewhere. On careful review of the radiographs at this hospital, the duodenojejunal flexure was noted to be on the right side of the midline in each case and a diagnosis of intestinal malrotation was confirmed at laparotomy. Both were relieved of their symptoms by repeat fundoplication accompanied by Ladd's procedure.

Gastric emptying is said to be slow in patients with idiopathic reflux[16] and more research is required to ascertain the role of delayed gastric emptying as an aetiological factor in reflux associated with anomalies such as malrotation. It is reported that the symptoms of reflux resolve after the problem of outlet obstruction has been corrected[7,8], but this is contrary to our experience. Of 18 infants and children over the age of 3 months who underwent Ladd's procedure alone for intestinal malrotation, vomiting persisted in 14 and an antireflux procedure was required. Outside the neonatal period, it is now our policy to consider treating children with significant reflux and intestinal malrotation with a combined antireflux operation and Ladd's procedure, as the latter operation does not always cure the reflux and the Nissen operation is dangerous and prone to failure in the presence of incomplete gastric outlet obstruction.

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Change of address

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Lack of necessity for corrections for pyloric losses and duodenogastric reflux in the performance of gastric secretory studies

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Gastric secretory studies are subject to considerable error owing to incomplete collections and to contamination by reflux of alkaline duodenal contents. Corrections for these sources of error have been defined, and they have been extensively applied in a research setting. In order to assess their utility in the performance of routine gastric secretory studies, the value of such corrections was assessed in 56 studies in patients with duodenal ulceration (10), previous surgical vagotomy (8), reflux oesophagitis (30) and primary oesophageal motility disorders (8). The effect of such corrections was small, and there were close correlations between uncorrected and corrected acid outputs in all four groups. The status of the vagal efferent gastric fibres was assessed by comparing the acid output after insulin hypoglycaemia with the maximal acid output after pentagastrin (insulin:pentagastrin ratio). The application of the corrections did not alter the conclusion regarding the assessment of vagal status in 55 of the 56 studies performed. It is concluded that such corrections are not necessary in the routine performance of gastric secretory studies.

Keywords: Gastric secretion, pyloric loss, duodenogastric reflux, insulin:pentagastrin ratio

The assessment of gastric function by the measurement of gastric secretory capacity is subject to significant error. Incomplete collection of gastric juice, losses through the pylorus and reflux of duodenal contents into the stomach may all contribute to this error. In an attempt to correct for these factors, the use of a phenol red marker alone[1] or with measurement of electrolyte concentrations of the gastric aspirate has been advocated[2,3]. However, this requires a major commitment in time and equipment, and the resulting calculations are complex and usually require the use of a computer.

Despite the theoretical increases in accuracy which these corrections bring to the measurement of gastric secretion, the necessity for such corrections in routine gastric secretory testing has not been convincingly demonstrated.

As part of a wider study into vagal nerve function in patients with oesophageal disease, gastric secretory studies were performed in a series of patients with upper gastrointestinal disorders using the corrections outlined above. The results of these studies have been analysed to assess the importance of making such corrections.

Patients and methods

Patients

A total of 56 gastric secretory studies were performed in four groups of patients

Group A This consisted of 10 patients (all male) with a mean age of 40·9 years (range 24–60) with endoscopically proven chronic duodenal ulceration.

Group B. This consisted of 8 patients (6 male) with a mean age of 46·4 years (range 24–57) who had previously undergone surgical vagotomy (truncal vagotomy and drainage in 6, proximal gastric vagotomy in 2) for chronic duodenal ulceration. A recurrent ulcer was present in 2 patients, both of whom had had a truncal vagotomy.

Group C This consisted of 30 patients (21 male) with a mean age of 41·2 years (range 23–62) with reflux oesophagitis on endoscopy, confirmed by oesophageal biopsy.

Group D. This consisted of 8 patients (2 male) with a mean age of 37·1 years (range 23–58) with primary motility disorders of the oesophagus (7 with achalasia of the cardia, one with diffuse oesophageal spasm). In all the diagnosis had been confirmed by barium swallow and oesophageal motility studies.

All patients gave voluntary informed consent to inclusion in the study which was approved by the Ethical Committee of the University Hospital, Nottingham.

Methods

Performance of gastric secretion studies. Patients were studied after an overnight fast. They were forbidden to smoke for 12 h before the test and all medications likely to have an effect on gastric acid secretion were stopped at least 48 h beforehand The height and weight of each patient were recorded.

A 14 FG nasogastric tube with multiple side holes was modified by the addition of a small intraluminal tube for the delivery of phenol red[4]. The tube was passed pernasally and the position checked by means of the water recovery test[5] Phenol red marker was infused throughout the test at a constant rate of 15 ml/h from a greased glass syringe driven by an electrically powered syringe infusion pump. At the beginning and end of the study standard samples were obtained by allowing the pump to deliver phenol red through the connecting tubing into a container for 15 min. A further 15 min period, during which gastric aspirates were discarded, then elapsed to allow adequate mixing of phenol red with gastric secretion.

Basal gastric secretion was then collected for two periods of 15 min each by continuous hand suction At the end of the basal collection period, soluble insulin (0·2 units/kg body weight) was injected intravenously and gastric secretion was collected in the same manner for a further 2 h. Blood sugar levels were monitored over this period and a satisfactory hypoglycaemic response was assumed if the blood glucose level dropped to below 2·2 mmol/l (40 mg/dl). This was achieved in all studies reported here.

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On completion of the insulin test, patients were given pentagastrin (6 units/kg body weight) subcutaneously and gastric secretion was collected for a further hour. The volume of gastric juice aspirated over each 15 min period during the course of the study was recorded (V_{obs}).

Measurement of titratable acidity. The pH of the aspirated gastric juice was measured at room temperature with a Radiometer (Copenhagen) pH meter, which had previously been standardized using buffers of known pH. The solution was then titrated with 0·1 M sodium hydroxide to a pH of 7·0 using a Radiometer automatic titrator. Each sample of gastric juice was assayed at least twice until the results of the two estimations agreed closely, and the mean of the two values was used.

Measurement of phenol red. A stock solution of phenol red was prepared at regular intervals by a standard method[1]. Standard solutions and gastric samples were alkalinized and read spectrophotometrically in a Unicam SP 600 spectrophotometer at 550 nm (at which the absorption of phenol red is maximal) and at 410 nm (at which the absorption of blood and bile is maximal, but the absorption of phenol red is minimal). The readings were then corrected for the presence of blood and bile in gastric juice[6].

Electrolyte concentrations in gastric juice. Sodium and potassium photometric readings were made on an EEL flame photometer with the appropriate filter after standardization with solutions of known concentration. Chloride concentrations were measured on a previously standardized EEL chloride meter.

Calculation of gastric secretory volumes. In order to calculate the true volume of gastric secretion (V_g), the total volume of dilution of the phenol red (V_{tot}) was obtained from the ratio of concentrations of phenol red in the sample and in the standard[2]. The volume of phenol red infusate contributes to this volume and therefore corrected volume (V_{corr}) is $V_{tot} - 3.8$ ml per 15 min.

Pyloric losses may be calculated for each 15 min period by the formula $V_{obs} \times (1-R)/R$ where R is the fraction of phenol red recovered[2].

The electrolyte concentrations are measured on aspirates to which the essentially electrolyte-free phenol red infusate is a contributor. Electrolyte values (including titratable acidity) were therefore multiplied by (V_{tot}/V_{corr})[7]. Each sample was checked for its adherence to the formula:

$$[H^+]+[Na^+]+[K^+]=[Cl^-]$$

and any sample which deviated by more than 4 mmol/l was rechecked until the formula balanced.

Duodenogastric reflux (V_r) was calculated for each 15 min period from the formula[3]:

$$V_r = 0{\cdot}00734 \times [Na^+] \times V_{corr} - 0{\cdot}0712 \times V_{corr} - 1{\cdot}281$$

The true volume of gastric secretion is therefore:

$$V_g = V_{corr} - V_r$$

Calculations of gastric acid output. Uncorrected acid outputs were obtained by multiplying observed volumes and titratable acidity. Corrected acid outputs were obtained by multiplying V_g by corrected titratable acidity. Titratable acidity was corrected by multiplying by V_{tot}/V_{corr} as indicated above. Basal acid output was taken as twice the sum of the values obtained from the two basal 15 min samples, the peak acid output after insulin was taken as twice the sum of the two highest consecutive 15 min samples after hypoglycaemia, and maximal acid output after pentagastrin as the sum of the four 15 min samples obtained after pentagastrin.

Statistical analysis. Correlations between corrected and uncorrected values were calculated by the least squares method. As gastric secretory data are not normally distributed, differences between groups were compared using a Mann–Whitney U test.

Results

Gastric acid output

The results of both uncorrected and corrected acid outputs for each secretory period are shown in *Table 1*. The effect of the corrections on basal acid output was small, altering the mean for each group by <1 mmol/h. After insulin, the acid output in the vagotomy group was increased by 2·1 mmol/h, but the mean correction overall was <1 mmol/h. Corrections for maximal acid output after pentagastrin were slightly greater (mean 1·5 mmol/h), with the greatest correction observed in the vagotomy group (3·5 mmol/h).

The effect of the corrections was not purely inflationary. Of the 168 corrections performed, 85 resulted in an increase in calculated acid output while 83 resulted in a decrease. The magnitude of the corrections ranged from 0 to 24·3 mmol acid/h but the majority were small: 76 (45 per cent) of the corrections were <1 mmol acid/h while 112 (67 per cent) were <2 mmol acid/h. Only 29 (17 per cent) of the corrections resulted in a difference between corrected and uncorrected values of >4 mmol acid/h.

There were significant correlations between corrected and uncorrected values. For basal acid output the correlation coefficient was 0·96 ($P<0{\cdot}001$; corrected value $= 0{\cdot}23 + 1{\cdot}02 \times$ uncorrected value), while for peak acid output after insulin the correlation coefficient was also 0·96 ($P<0{\cdot}001$, corrected value $= 0{\cdot}05 + 1{\cdot}04 \times$ uncorrected value). There was also a close correlation for maximal acid output after pentagastrin ($r=0{\cdot}91$; $P<0{\cdot}001$; corrected value $= 2{\cdot}59 + 0{\cdot}95 \times$ uncorrected value).

There was also a significant correlation between gastric acid output and the magnitude of the correction applied ($r=0{\cdot}55$; $P<0{\cdot}001$; correction $= 0{\cdot}61 + 0{\cdot}13 \times$ gastric acid output), indicating that the greatest alterations tended to be made at the highest levels of gastric secretion.

Duodenogastric reflux and pyloric losses

Using these methods it is possible to calculate both amounts of duodenogastric reflux and pyloric losses. It is unlikely that either of these measurements is physiologically representative

Table 1 *Mean uncorrected and corrected acid output values in the four groups of patients studied*

		Patient group			
Acid output (mmol/h)		A	B	C	D
Basal	U	7·0	3·3	2·1	4·0
		(0–26)	(0–8·1)	(0–10·0)	(0–15·8)
	C	7·0	2·5	2·2	3·4
		(0–29·8)	(0–5·8)	(0–12·8)	(0·1–13·0)
Peak after insulin	U	33·6	12·9	15·9	14·3
		(14·0–54·4)	(0–17·7)	(2·0–43·0)	(5·2–32·4)
	C	35·5	15·0	15·8	15·8
		(15·8–59·6)	(0–21·1)	(1·6–40·1)	(4·9–29·2)
Maximal after pentagastrin	U	35·0	17·6	23·1	15·1
		(11·4–66·3)	(1·9–66·3)	(6·8–42·8)	(6·6–27·6)
	C	37·2	21·1	23·8	16·4
		(15·5–52·7)	(1·6–72·0)	(5·9–43·8)	(5·6–28·4)

Mean values and ranges. U, uncorrected; C, corrected; group A, endoscopically proven duodenal ulcer; group B, surgical vagotomy for chronic duodenal ulcer, group C, reflux oesophagitis, group D, primary motility disorders of the oesophagus

Table 2 *Mean duodenogastric reflux and pyloric loss for the differing periods of acid secretion in the four groups of patients studied*

	Patient group			
Study period	A	B	C	D
Recovery of phenol red	0·85 (0·78–0·95)	0·82 (0·75–0·92)	0·81 (0·74–0·98)	0·84 (0·77–0·94)
Duodenogastric reflux (ml/h)				
Basal	27·5 (3–51·6)	27·5 (10·0–58·0)	28·8 (5·4–88·0)	13·7 (2·0–31·4)
After insulin	17·0 (1·8–46·0)	18·0 (5·8–34·6)	21·5 (0–93·8)	16·0 (1·6–39·6)
After pentagastrin	12·8 (0–27·9)	33·4* (0–85·7)	19·5 (0–104)	20·2 (16·3–74·2)
Pyloric loss (ml/h)				
Basal	46·5 (0–110)	23·8 (0–71·6)	36·2 (0–84·8)	33·7 (3·4–77·4)
After insulin	30·7 (2·4–79·8)	27·8 (0–97·4)	41·0 (0–117)	25·3 (8·4–46·4)
After pentagastrin	69·1 (0–131)	65·0 (20·0–97·1)	58·6 (0–105)	37·1 (16·3–74·2)

*Duodenogastric reflux in the vagotomy group after pentagastrin is significantly greater than in unoperated duodenal ulcer patients ($P = 0.02$; Mann–Whitney *U* test). Group A, endoscopically proven duodenal ulcer, group B, surgical vagotomy for duodenal ulcer, group C, reflux oesophagitis; group D, primary motility disorders of the oesophagus

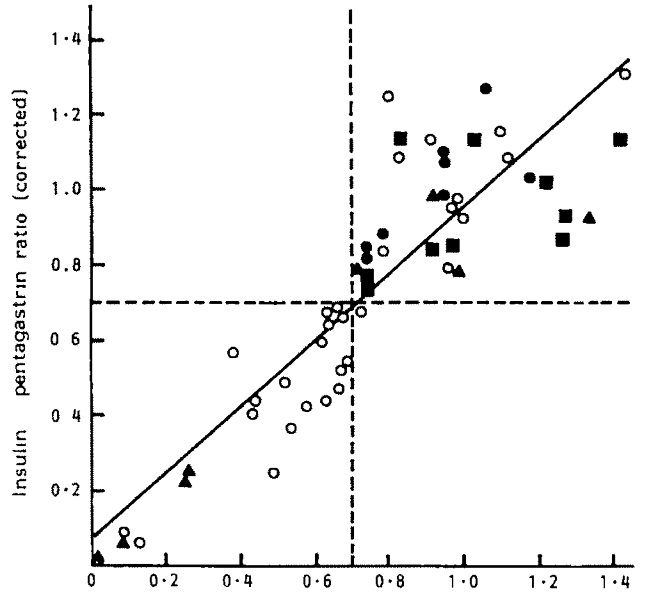

Figure 1 *Relationship between uncorrected and corrected insulin pentagastrin ratios in the four groups of patients studied.* ■, *duodenal ulcer,* ▲, *surgical vagotomy,* ○, *oesophagitis;* ●, *primary oesophageal motility disorders The dotted lines represent the lower limit of normal and the solid line the regression equation between the two values*

in view of the continuous removal of gastric secretion, but they might none the less be of value in the assessment of differing states of gastric secretion or in different groups of patients. Values for both were calculated for the same periods of gastric secretion as were the acid output figures and the results are shown in *Table 2*.

Similar results were seen in all four groups and with one exception in all study periods. The amount of duodenogastric reflux in the pentagastrin-stimulated period was significantly higher in the surgical vagotomy group than in the duodenal ulcer group ($P = 0.02$; Mann–Whitney *U* test). This is presumably the result of the drainage procedure performed in association with the vagotomy.

Insulin: pentagastrin ratio

Previous studies have demonstrated that the ratio of the peak acid output after insulin to the maximal acid output after pentagastrin is a suitable test of efferent vagal fibres to the stomach and that normal vagal function is associated with a level of 0·7 or greater[8]. Approximately half the patients with reflux oesophagitis have a value below this[9] while patients with achalasia have normal ratios[10]. The values in those studies were obtained by using corrected values.

Analysis of the relationship between insulin:pentagastrin ratios obtained by using corrected and uncorrected acid outputs revealed a close relationship between the two, irrespective of whether corrections were applied (*Figure 1*; $r = 0.88$; $P < 0.001$; corrected $= 0.072 + 0.88 \times$ uncorrected). There was a high degree of concordance between corrected and uncorrected values. In only one patient was an uncorrected value above 0·7 changed to a corrected value below 0·7 (0·73 uncorrected; 0·68 corrected).

Discussion

The application of corrections using a phenol red marker and calculation of electrolyte concentrations requires, in addition to the measurement of titratable acidity, a further five chemical or spectrophotometric measurements with a total of nine mathematical calculations on each sample. Furthermore, phenol red deteriorates with time, and each study requires re-analysis on the completion of all the tests performed with a particular phenol red stock bottle[2]. The measurements are expensive in terms of technician time and equipment and the mathematical calculations are complex and tedious unless performed on a computer. Such an effort can therefore be justified on a routine basis only if it produces significant alterations in the uncorrected gastric output values.

The results of this study indicate that there are close correlations between the values obtained by both methods for all three periods of gastric secretion studied. The value of the corrections was small, being greatest with higher acid outputs, where it is least likely to produce any change in the appreciated secretory status of an individual patient. In addition, the slope of all three correlations was close to unity and, for both basal acid output and peak acid output after insulin, the intercept was close to zero, further suggesting that, for these periods of gastric secretion, such corrections will have minimal effect.

Gastric secretions in this study were collected by continuous hand aspiration. This is the most effective method for ensuring complete collection[11] and it may be that collection errors were therefore minimized. The same results might not be obtained if a pump were used for collection purposes. However, should this be the case, it would seem more cost effective to convert to hand suction than to perform these costly and complex corrections.

The method described here allows for the separate calculation of pyloric loss and duodenogastric reflux. There may be considerable variation in these volumes in consecutive 15 min collection periods and they were therefore averaged over similar periods to those selected for gastric acid secretion. However, it is misleading to think that these give any underlying physiological clue to events in the normal stomach because under the conditions of a gastric secretory study gastric dynamics are upset by the aspiration of most of the secretion. With these reservations, it might be worth calculating these volumes if there were significant differences between groups or between secretion periods. This did not prove to be the case, the only significant difference being observed in those patients who had had surgical procedures which had disrupted or bypassed the pylorus. In these patients the amount of duodenogastric reflux was increased after pentagastrin stimulation. An increase in such reflux in patients with gastrojejunostomies (but not pyloroplasties) after insulin had previously been observed[3]. In this study the number of patients with gastrojejunostomies was too small to confirm or refute this but we did not find that the increased amount of duodenogastric reflux significantly altered conclusions regarding vagal status in these patients.

Previous studies using these corrections have involved mainly patients with duodenal ulcer before and after vagotomy[12,13], and it has been advocated that the best single criterion for the assessment of vagal function is the volume response after insulin. without taking the basal or pentagastrin states into consideration. Such an approach is, however, not applicable to patients without duodenal ulceration (it is only necessary to consider the example of gastric secretion in Addisonian pernicious anaemia) and it is therefore necessary to take parietal cell mass into consideration. We have therefore used the insulin:pentagastrin ratio as an index of gastric efferent vagal function The use of a ratio also means that fixed errors in measurement are minimized and that variation in parietal cell mass with height[14,15] and sex[16] is accounted for.

A ratio of 0·7 or over is indicative of an intact gastric vagal supply[7], and agrees with the normal ratio of 0·7 found by Boulos[17] when comparing insulin volume outputs with those after histamine infusion. We found a normal value in 33 studies, irrespective of whether uncorrected or corrected values were used. Twenty-two of the remaining studies provided ratios of less than 0·7, irrespective of corrections, and in only one case was there discrepancy between the ratios obtained by the two methods. The use of such a ratio is therefore independent of corrections (an observation made by Boulos[17] but not pursued) and appears to be a useful method of assessing vagal function. A similar ratio had previously been shown to be of value in the management of patients with recurrent ulceration after surgery[18].

Overall, the results of this study indicate that application of corrections for pyloric loss and duodenogastric reflux (even in patients who had undergone surgery which had disrupted or bypassed the pylorus) fails to produce significant alterations in the values obtained by conventional methods and do not support the routine use of such corrections in studies of gastric secretory function.

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Implication of duodenogastric reflux in the pathogenesis of Barrett's oesophagus

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Fasting and postprandial intragastric bile acid concentrations have been estimated and compared in patients with complications of Barrett's oesophagus, patients with Barrett's oesophagus without complications, patients with oesophagitis and a group of normal subjects who acted as controls. There was no significant difference in fasting intragastric bile acid concentrations between the groups. Postprandial bile acid concentrations were significantly greater in the patients with complications of Barrett's than in the remaining groups at 60, 90 and 120 min. Significant concentrations of bile acids were seen in gastric juice of unaltered pH and may be undetected on intra-oesophageal pH monitoring. Duodenogastric reflux may be implicated in the pathogenesis of complications of Barrett's oesophagus.

Keywords: Barrett's oesophagus, complications, duodenogastric reflux, bile acids

Barrett's oesophagus is a condition in which, in a variable segment of the oesophagus, the normal squamous epithelium becomes replaced by columnar epithelium. The development of a columnar-lined oesophagus is believed to be secondary to gastro-oesophageal reflux[1]. Both clinical and experimental studies support a causal relationship between acid reflux and columnar-lined oesophagus[2–6]. Prolonged intra-oesophageal pH recordings have established that the patterns of acid reflux in Barrett's oesophagus display a markedly increased number of acid events and more prolonged clearance times of acid when compared with patients presenting with oesophagitis without the presence of columnar epithelium[7,8]. Poor correlation is known to exist between the frequency of acid reflux, duration of acid contact time and the response of the oesophageal mucosa to injury[9].

Patients with Barrett's oesophagus may present with, or develop, complications such as Barrett's strictures, or Barrett's ulcers and are at an increased risk of developing oesophageal adenocarcinoma. The development of such complications does not appear to correlate well with either duration of reflux symptoms or severity of acid reflux on 24 h pH monitoring[10]. It appears that acid reflux alone may not be sufficient to account for the development of complications which may occur in the columnar–lined oesophagus. It has been postulated[11] that a further insult to the oesophageal mucosa other than acid may account for the development of complications in this condition.

To test the hypothesis that complications of a columnar-lined oesophagus are associated with excessive duodenogastric reflux of bile acids, a study of patients with a columnar-lined oesophagus both with and without complications has been undertaken.

Patients and methods

Eighteen patients with Barrett's oesophagus have been studied. A diagnosis of Barrett's oesophagus was accepted only on histological confirmation of columnar epithelium, extending more than 5 cm at endoscopy above the gastro-oesophageal junction. The age range of the patients was from 34 to 81 years (mean 65·0 years). All had symptoms of gastro-oesophageal reflux which varied from 4 months to 10 years (median 2 years). There were 11 patients with complications of Barrett's (CB) and 7 with uncomplicated Barrett's (UB). In the complicated group, seven patients had strictures, one of whom had severe dysplasia on histological sectioning; three patients had Barrett's ulcers, one of whom also had a Barrett's stricture. The Barrett's ulcers were present in the columnar epithelial segment. One patient had an adenocarcinoma histologically proven on biopsy in the Barrett's mucosa in the complicated Barrett's group. This adenocarcinoma was diagnosed during endoscopic follow-up surveillance for known Barrett's oesophagus. For the purposes of this study all medication likely to affect gastrointestinal motility or gastric acid secretion was stopped for 72 h before the study. Patients who had undergone upper gastrointestinal tract surgery or biliary surgery were excluded from the study. The presence of gallstones was excluded by ultrasound examination, cholecystogram, or at subsequent laparotomy in all patients.

Five patients with erosive (grade 3) oesophagitis were also studied. The age range in this group was from 44 to 62 years (mean 51 years) and duration of symptoms in this group varied from 2 months to 2 years (median 8 months). Patients who previously had undergone upper gastrointestinal tract surgery or had biliary tract disease were excluded from this group. Nine healthy asymptomatic unmatched control subjects were also studied.

Informed consent was obtained from all patients and controls and Ethical Committee approval was granted for this study. In the fasting patient a size 14 Salem sump suction tube was introduced *per nares* and located in the body of the stomach and its position determined radiologically. A 45 min accommodation period was then allowed; subsequently, gastric contents were aspirated and discarded. A 30 min aspiration period was then started using low-pressure suction (100 cmH_2O) and intermittent manual aspiration of the tube. The gastric juice obtained during this 30 min aspiration period was taken as a true fasting gastric aspirate. At the end of the 30 min period a test meal containing 18 g corn oil and 12 g glucose made up to 100 ml with warm water was administered through the nasogastric tube as described by Collins *et al.*[12]. Samples of gastric juice (10 ml) were aspirated at 20, 40, 60, 90 and 120 min postprandially. All subjects remained semirecumbent during the study period and the study was well tolerated in all instances. At the end of the study period, the stomach was completely emptied and the suction tube removed. Gastric juice samples were centrifuged at 1500 *g* and 4°C for 15 min to separate corn oil and mucus from the aqueous portion. Intragastric bile acid concentrations in the gastric juice aspirates were assayed using an enzymatic technique[13]: this involves the enzymatic reduction by 3α-hydroxy steroid dehydrogenase of bile acids to corresponding ketosteroids, with reduction of NAD to $NADH_2$. The $NADH_2$ is produced mole for mole from bile acids and may be quantified using a spectrophotometer set to absorb at 340 nm. The validity of this technique using a corn-oil-based test meal has been verified previously[14]. Samples (100 μl) were analysed after the pH had been adjusted to 9·5. The lowest concentration of bile acids which could be determined accurately was 10 μmol/l. Each gastric aspirate was assayed in duplicate and known concentrations of glycocholic acid were assayed with each run of samples to check the linearity of the assay. The coefficient of correlation of the assay was 0·98. The day-to-day variation of the assay was determined by assaying a high and low control sample with each assay, in duplicate. The coefficients of variation were 7·5 per cent and 6·3 per cent respectively for high and low values

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All patients underwent prolonged intra-oesophageal pH monitoring (24 h) using Synectics pH probe and Digitrapper. An acid reflux event was defined as a fall in pH to 4 or less for 5 s or longer. Data were analysed using Synectics Software and an Apple Computer The pH studies (24 h) were analysed according to total number of reflux events, duration longer than 5 min and total percentage time spent at pH 4 or less.

Statistical analysis between the groups for both intragastric bile acid concentrations and 24 h pH scores, were by Wilcoxon signed rank tests for non-parametric data.

Results

Fasting and postprandial pH values

All patients and volunteers had at least one gastric aspirate of pH 3·5 or less, although occasional high intragastric pH values were recorded in all groups. No significant differences between pH values during fasting or during any postprandial period were demonstrated between patients with or without complications of Barrett's oesophagus, oesophagitis patients or control subjects.

Intragastric bile acid concentrations

No significant difference was demonstrated between any of the study groups in intragastric bile acid concentrations during the fasting period (*Table 1*). Similarly, at 20 and 40 min postprandially no significant difference in intragastric bile acid concentrations was demonstrated between the groups.

At 60 min postprandially, intragastric bile acid concentrations were significantly greater in the complicated Barrett's patients ($P < 0{\cdot}01$) than in any of the other three groups studied (*Figure 1*). Significantly elevated intragastric bile acid concentrations were also seen in the complicated Barrett's group at 90 and 120 min ($P < 0{\cdot}05$).

Postprandial pH of gastric juice

Table 2 illustrates the mean pH value at each postprandial period studied and demonstrates intragastric bile acid concentrations in each. It will be noted that two patients demonstrated intragastric bile acid concentrations in excess of 1 mmol/l and yet had intragastric pH values of less than 4—the value to which the pH must fall before an 'acid' reflux event is recorded on ambulatory pH monitoring. The residual volumes obtained at the end of the study period upon aspiration of the sump tube did not differ significantly between the patient groupings or control subjects.

Ambulatory 24 h pH scores

Ambulatory 24 h pH monitoring showed no significant

Table 1 *Fasting and postprandial intragastric bile acid concentration at 20 and 40 min in each study group*

Group	Fasting	Postprandial (min) 20	40
Complicated Barrett's (*n* = 11)	25 (0–109)	25 (0–2692)	187 (0–1417)
Uncomplicated Barrett's (*n* = 7)	0 (0–266)	17 (0–184)	17 (0–184)
Oesophagitis (*n* = 5)	0 (0–80)	10 (0–330)	80 (0–80)
Controls (*n* = 9)	22 (0–109)	47 (0–3137)	40 (0–398)

The median and range values are given in μm/l. Wilcoxon rank sum test: differences between groups not significant

Table 2 *Intragastric pH values at 60, 90 and 120 min postprandially*

Group	Postprandial (min) 60	90	120
Complicated Barrett's (*n* = 11)	3·1 (1·5–4·6)	2·5 (1·2–4·0)	2·1 (1·2–5·1)
Uncomplicated Barrett's (*n* = 7)	3·3 (2·0–4·8)	2·7 (1·4–4·1)	2·4 (1·4–4·0)
Oesophagitis (*n* = 5)	3·7 (2·0–4·2)	2·7 (1·6–3·9)	2·0 (1·6–4·0)
Controls (*n* = 9)	3·9 (2·1–6·2)	3·5 (1·8–6·7)	2·9 (1·6–6·6)

The mean and range values are given. Wilcoxon rank sum test. differences between groups not significant

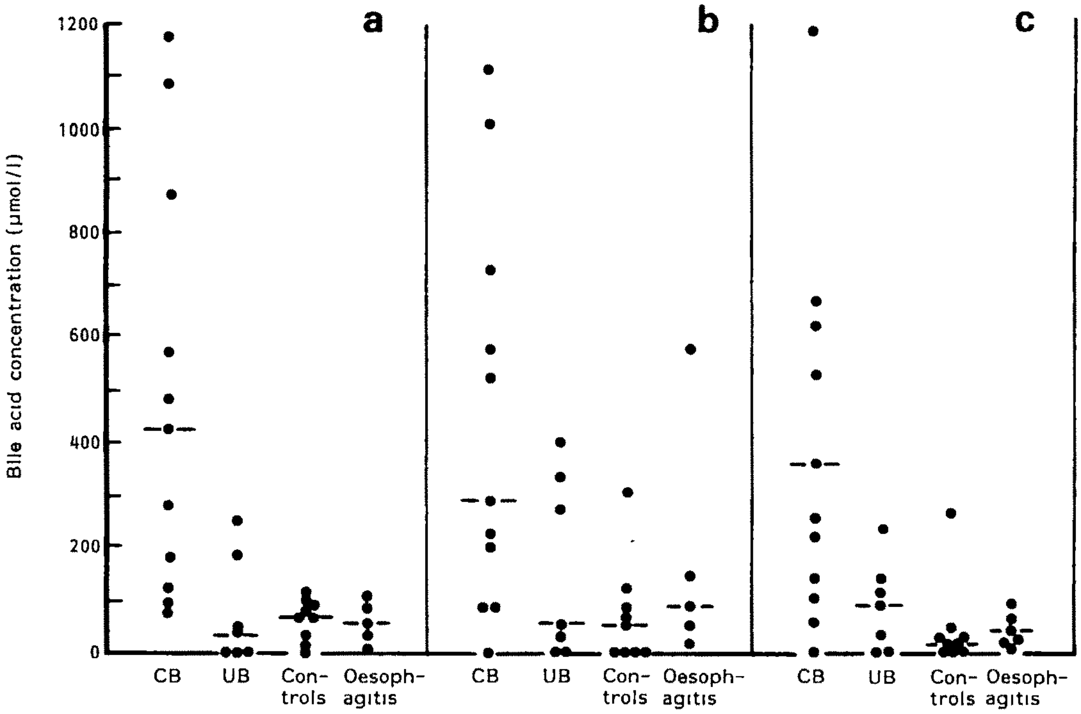

Figure 1 *Intragastric bile acid concentrations at* **a**, *60*, **b**, *90 and* **c**, *120 min postprandially, in each study group (μm/l, median ± range) Wilcoxon rank sum test* **a**, $P < 0{\cdot}01$, **b**, $P < 0{\cdot}05$; **c**, $P < 0{\cdot}05$, *complicated Barrett's oesophagus (CB) versus uncomplicated Barrett's oesophagus (UB), oesophagitis and controls*

Table 3 *pH measurement (24 h) in patients with and without complications of Barrett's oesophagus, and in oesophagitis patients*

	Complicated Barrett's ($n=11$)	Uncomplicated Barrett's ($n=7$)	Oesophagitis ($n=5$)
Total number of reflux episodes	53 (5–195)	44 (8–133)	20* (1–62)
Percentage time pH ⩽ 4	30·3 (6·4–75·2)	32·3 (2·8–73·8)	7·1† (1·0–16·8)
Number of reflux episodes lasting > 5 min	9 (3–24)	11 (0–25)	4* (0–8)

The median and range values are given. Wilcoxon rank sum test; *$P<0·01$, †$P<0·001$

difference in either total number of reflux events, number of events lasting longer than 5 min, or total percentage of time with pH ⩽ 4 between patients with or without complications of Barrett's oesophagus (*Table 3*). Each of the two groups of patients with Barrett's oesophagus, however, had greater exposure to acid than did the oesophagitis group alone.

Discussion

Duodenogastric reflux of bile has been implicated in the development of oesophagitis[15,16]. This evidence was based on intubation studies which have come under criticism since the advent of non-invasive radio-isotope scanning. It has been argued that intubation studies produce false-positive results in relation to duodenogastric reflux[17]. Advocates of non-invasive methods of documenting duodenogastric reflux point out that intubation may alter the 'oesophagogastroduodenal axis'[18], whereas others argue that the placement of a transpyloric tube produces no disturbance in duodenogastric reflux in healthy volunteers and that isotopic imaging of duodenogastric reflux has limitations[19]. In view of these controversies the precautions taken by Collins *et al.*[12], of allowing an accommodation period before gastric aspiration is started, is a significant improvement on earlier intubation studies and has been adopted in this study. Using this technique we have demonstrated that fasting intragastric bile acid concentrations are not elevated either in patients or in healthy volunteers, as has been reported previously[12]. This study was undertaken in patients with complications of a columnar-lined oesophagus including stricture formation, ulcer formation and, in one patient, the development of neoplasia—subjects previously not studied in this fashion. Clinically, these complications are not infrequently seen in combination, which could signify a similar underlying aetiology. The demonstration of raised intragastric bile acid concentrations in this group when compared with patients with a columnar-lined oesophagus free from complications, or in oesophagitis patients without Barrett's oesophagus and in control subjects, has not been previously demonstrated.

Bremner[11] has argued that, as the columnar-lined oesophagus is most likely to be a protective response of oesophageal mucosa to acid reflux, it is unlikely that further acid reflux would then cause ulceration in the already supposedly acid-resistant segment. He has postulated that bile reflux may be involved in the pathogenesis of Barrett's ulceration. The data from this study would support such a hypothesis. Were acid reflux alone to be implicated in the development of Barrett's ulcers, strictures and neoplasia, then significant differences would be expected on 24 h pH monitoring between Barrett's patients. This study has demonstrated that although differences may exist between groups of patients with Barrett's oesophagus, the development of complications is not dependent on acid reflux. This study suggests that duodenogastric reflux of bile acids into the stomach occurs with greater frequency in patients with complications of Barrett's oesophagus, as the higher concentrations found postprandially are unlikely to have resulted from delayed gastric emptying or increased gastric secretion because the stomach was empty at the start of the study and residual volumes did not differ significantly between the study groups at the end of the study. This would imply that no gross abnormality in gastric emptying or secretion was occurring in one group more than in another. As demonstrated in this study, refluxate containing (in some instances) markedly elevated intragastric bile acid concentrations, may find its way into the lower oesophagus and be undetected on ambulatory 24 h pH monitoring, because the pH of gastric juice remains low. By prolonging the intubation period (up to 2 h postprandially) we have demonstrated that elevated intragastric bile acid concentrations may exist in some Barrett's patients for up to 2 h after meals, a fact which has hitherto been unrecognized 'Alkaline reflux', reported in previous studies of the pathogenesis of oesophageal mucosal damage[20], may be a misnomer because the cytotoxic effect of refluxates may not be inferred on the basis of 24 h acid monitoring alone. At an acid pH, bile acids which are unconjugated precipitate, but conjugated bile acids—which are commonly present in the duodenum—remain in solution in an acid pH and may damage the oesophageal mucosa.

The demonstration of significantly elevated intragastric bile acid concentrations in patients with complications of Barrett's oesophagus raises the possibility that these patients demonstrate a diffuse motor abnormality of the upper gastrointestinal tract, which may not be limited to the lower oesophageal sphincter but may also involve the pylorus. Although studies of gastric emptying in Barrett's oesophagus have failed to demonstrate prolonged emptying[21], it may be that uncoordinated motility in such patients produces abnormal duodenogastric reflux which is undetectable on 24 h pH monitoring, but is potentially cytotoxic.

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Simple method of closing a para-ileostomy fistula

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Para-ileostomy fistula formation occurs in 2–14 per cent of patients who undergo colectomy or proctocolectomy and ileostomy formation for inflammatory and non-inflammatory disease[1–5]. It is more common in Crohn's disease but occurs in non-granulomatous disease especially if seromuscular stitches are used to secure ileum to the abdominal wall, or if a poorly fitting rigid flange is used on the ileostomy appliance[6]. Such fistulae make management of a stoma difficult or impossible for the patient and in the past further surgery was considered the only way of correcting the problem[1,3,5,6]. A simple non-operative method has been used in three patients with a para-ileostomy fistula, with successful closure in two.

Patients and methods

Patient 1

A 67-year-old man with a 2-year history of total ulcerative colitis, resulting in intractable diarrhoea, underwent a panproctocolectomy and ileostomy He made an uneventful postoperative recovery, but when reviewed in the outpatient department 6 weeks later had developed a skin level para-ileostomy fistula. Probing demonstrated a narrow fistula which entered the ileal lumen at the level of the abdominal wall musculature

Patient 2

A 53-year-old woman with a long history of scleroderma was referred with a 2-year history of increasing constipation. Rectal and colonic biopsies showed fibrosis of the muscularis, compatible with involvement by scleroderma. Eventually she was unable to evacuate her bowel at all without regular enemas and chose to have a defunctioning ileostomy She made a good postoperative recovery but when reviewed in the outpatient clinic 6 weeks later complained of leakage from beneath the Stomahesive (Squibb Surgicare Ltd , UK) seal of her appliance Inspection revealed a skin level para-ileostomy fistula

Patient 3

A 63-year-old man who had undergone an abdominoperineal excision of a rectal carcinoma 9 years previously developed adenomatous polyps throughout his remaining colon. Biopsies showed dysplastic changes and a total colectomy and end ileostomy was therefore performed. Postoperative recovery was uneventful but when reviewed in the outpatient clinic 6 weeks later the patient complained of a discharge around his stoma Examination revealed a narrow para-ileostomy fistula which opened into the ileum just deep to the abdominal wall

The fistula of all three patients was treated in the same way A pipe cleaner was used to clean the fistula and by aggressive rubbing the lining of the fistula was abraded. The surrounding skin and mucosa were liberally covered with petroleum jelly to protect them from accidental spillage of phenol A pipe cleaner was then soaked in 6 per cent aqueous phenol, wiped free of excess fluid and gently placed into the full length of the fistula for 1 min. The cleaner was then removed, the skin cleaned and a fresh stoma bag applied.

This simple procedure resulted in immediate cessation of leakage in patients 1 and 3 with healing of their fistula within a fortnight These fistulae have remained closed after 5- and 1-year follow-up, respectively. Patient 2 experienced a small amount of continued leakage which stopped immediately after a second application of phenol 2 weeks later. Initially it was thought that her fistula had healed but 3 months later she returned with a recurrence of the problem. At this stage it was decided to revise the ileostomy surgically.

Discussion

Although uncommon, a para-ileostomy fistula is a serious complication of ileostomy formation because it can make management of the stoma difficult for the patient and hitherto required an operation to correct the problem. This procedure is simple and safe, provided care is taken in handling the phenol. It can be performed as an outpatient procedure. It is presumed that the fistula heals due to de-epithelialization and subsequent fibrotic obliteration of the tract. It has not been used in patients with Crohn's disease as it is considered unlikely that a long-term cure would be effected. In patients with non-granulomatous disease who develop a narrow para-ileostomy fistula the above method is recommended as a first line of treatment

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Mesenteric infarction: an analysis of 83 patients with prognostic studies in 44 cases undergoing a massive small-bowel resection

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A series is presented of 83 patients surgically explored for massive bowel infarction. Old men with previous heart disease and symptoms of peripheral atherosclerosis were primarily affected. Clinical presenting features were abdominal pain (100 per cent), peritonitis (57 per cent), shock (34 per cent) and hypothermia (26 per cent). A third-space syndrome with metabolic acidosis and uraemia was the most common physiological derangement. Age was the only factor that appeared to have influenced the surgeon's decision to perform massive bowel resection (71 years in non-resected versus *64 years in resected patients,* $P<0\cdot006$*). The overall mortality rate was 71 per cent. Forty-four patients underwent massive bowel resection (mean length of remaining small bowel 60±40 cm) and twenty-four (54 per cent) survived the procedure. Axillary temperature was higher in survivors (36·7°C* versus *36·1°C,* $P<0\cdot03$*). Early postoperative total plasma protein and albumin concentrations were also higher in survivors (57* versus *46 g/l,* $P<0\cdot005$*; 27* versus *22 g/l,* $P<0\cdot02$*). Patients with previous symptoms of atherosclerotic disease and high pre-operative blood urea levels also had a bad prognosis. Survivors had a mean hospital stay of 57 days and parenteral nutrition had to be maintained for a mean of 34 days. The survival rate achieved with massive resection justifies this surgical approach in selected patients with massive bowel infarction.*

Keywords: Bowel resection, mesenteric infarction

Mesenteric infarction remains a very difficult therapeutic problem and its prognosis continues to be poor with an overall mortality of about 80 per cent[1–5]. Vascular techniques have not helped much in its treatment, with the exception of the minority of patients who have superior mesenteric artery embolism[1,6,7]. At laparotomy it is still very common to find necrotic bowel requiring extensive resection.

Important advances in our understanding of the process of small-bowel adaptation[8], in the treatment of acute digestive failure with parenteral nutrition[9,10] and in the management of patients with short gut syndrome[11] have made surgeons more aware of the curative potential of massive bowel resection (MBR). In 1975 we began treating patients with mesenteric infarction not deemed to be moribund with MBR and subsequent parenteral nutrition. Here we report our results in a consecutive series of 83 patients found at laparotomy to have mesenteric infarction during the last 10 years in our two institutions. Particular emphasis is given to the factors influencing the surgeon's therapeutic decision and to outcome in the subgroup of 44 patients who underwent MBR. As no large series of patients undergoing MBR for intestinal ischaemia has been reported, our experience may help to clarify the curative potential of such an approach.

Patients and methods

The records of 105 consecutive patients explored for mesenteric infarction at the Hospital de Nostra Senyora del Mar and the Hospital de Bellvitge in Barcelona, from January 1976 to June 1985, were reviewed. Twenty-two patients were excluded because they had non-massive bowel infarction. Eighty-three had massive infarction, defined as those cases in which less than 120 cm of small bowel were spared if colonic resection was not performed or less than 180 cm of small bowel were left if colectomy was carried out. These 83 patients form the basis of the present study.

The study was conducted in two parts. First, the clinical characteristics, laboratory data, radiological evaluation and operative findings of the whole series were analysed and a comparison was made between patients having resection and those undergoing simple exploratory laparotomy. In a second evaluation, the characteristics of the 44 patients undergoing MBR were studied and a comparative analysis was made between 24 survivors and 20 non-survivors. Hospital stay and parenteral nutrition requirements were assessed in the former. No specific mention is made of aortography or vascular surgical techniques because these were carried out in very few patients.

A Digital VAX 11/725 computer (Digital Equipment Company, USA) and the SPSS-X statistical programs package (SPSS Inc., USA) were used for the statistical analysis. Comparison between groups was carried out with the χ^2 test for qualitative variables and the Student's *t* test for comparisons of the means of quantitative values. Variables non-normally distributed were compared with the Mann–Whitney *U* test. Differences were regarded as statistically significant when $P<0\cdot05$ A stepwise discriminant analysis was also performed to identify the variables which had an influence on outcome after MBR

Results

Characteristics of the whole series

The mean age of patients presenting with mesenteric infarction was 67±s.d. 11 years. There were 53 (64 per cent) male and 40 (36 per cent) female patients. Most patients had factors that increased the risk of developing mesenteric infarction, or that could contribute to a poor outcome (*Table 1*). Symptoms or signs of peripheral atherosclerosis (i.e. previous cerebrovascular

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Table 1 *Past medical history, presenting symptoms, aetiology and pre-operative laboratory results in 83 cases of massive mesenteric infarction*

	No. of cases	Percentage
Past medical history		
Ischaemic heart disease	17	20
Valvular heart disease	15	18
Arrhythmia	25	30
Other features of atherosclerosis	33	40
Respiratory diseases	16	19
Other	32	39
Presenting symptoms and signs		
Peritonitis	47 (83)*	57
Bloody diarrhoea	19 (83)	23
Shock	28 (83)	34
Fever (> 37°C)	10 (54)	19
Tachycardia (> 90 beats/min)	41 (61)	67
Aetiology		
Arterial thrombosis	19	23
Venous thrombosis	7	8
Arterial embolism	6	7
Non-occlusive ischaemia	3	4
Unknown	48	58
Pre-operative laboratory results	mean ± s.d.	range
BUN (mg/100 ml)	61·6 ± 48	5–276
Haematocrit (%)	46·0 ± 8	12–65
Leucocyte count ($\times 10^9$/l)	16·9 ± 8	3–42
Venous blood pH	7·34 ± 0·1	6·9–7·5
Base excess	−7·1 ± 7·3	−24–8
Standard bicarbonate	17·4 ± 6	7–31·5
P_{CO_2} (mmHg)	31·9 ± 12	10–74

BUN, blood urea nitrogen; * number of cases in which the information was available

accidents or intermittent claudication) other than coronary heart disease were present in 40 per cent of the patients. All patients complained of abdominal pain on admission. Presenting symptoms and physical signs are shown in *Table 1*. Few patients (19 per cent) had fever and, in fact, axillary temperature was lower than 36°C in 14 cases (26 per cent of the patients in whom temperature readings were available). Mean temperature was 36·5 ± 0·8°C (range 35–38·3°C) and did not correlate with other signs reflecting shock. Pre-operative laboratory results are also shown in *Table 1*. Blood urea nitrogen and the haematocrit were above the normal range in 59 per cent of the patients. Leucocytosis over 15×19^9 cells/l was observed in 58 per cent of cases. Venous blood pH values were recorded in 32 patients: 24 had metabolic acidosis and 8 showed metabolic alkalosis. Plain abdominal films were normal in 21 per cent of the patients, minor abnormalities were found in 24 per cent and marked ileus was evident in 55 per cent of cases.

At laparotomy, the cause of mesenteric infarction could be ascertained in only 35 patients (42 per cent) (*Table 1*). Superior mesenteric artery thrombosis was the most common underlying vascular disease. In the remaining cases a probable cause was suspected but not firmly established, because of the advanced degree of bowel necrosis and distal vessel thrombosis. Intestinal perforation was observed in 11 (13 per cent) of cases. The mean length of uninvolved bowel was 60·7 ± 40 cm in resected and 54·4 ± 112 cm in non-resected patients, respectively.

A comparison of clinical and biochemical values between patients undergoing MBR ($n = 44$) and patients having only exploratory laparotomy ($n = 39$) is shown in *Table 2*. Age was the only significant difference between both groups, resected patients being, on average, 7 years younger. Overall mortality rate in the 83 patients was 71 per cent; all 39 patients undergoing only laparotomy died.

Prognosis and survival after MBR

Forty-four patients (29 men and 15 women) underwent MBR and 24 (54 per cent) survived the procedure and were discharged from the hospital. *Table 3* shows their past medical history. Although the difference did not reach statistical significance, previous symptoms or signs of atherosclerosis were more common in non-survivors. *Table 4* presents the main features of the 44 resected patients. No significant difference was found in the delay between admission and MBR when survivors and non-survivors were compared. Axillary temperature was significantly higher in survivors, none of whom had a temperature below 36°C (range 36–38·3°C), whereas 73 per cent of non-survivors had temperatures below 36·5°C (*Figure 1*). Discriminant analysis showed that a pre-operative temperature of 36·5°C allowed a correct differentiation between survivors and non-survivors in 68 per cent of cases. Pre-operative blood urea nitrogen levels were higher in non-survivors although this difference did not reach statistical significance.

The aetiology of mesenteric infarction could be ascertained in 23 of these 44 patients (*Table 4*). Although none of the differences reached statistical significance, the incidence of mesenteric artery thrombosis was lower and that of venous thrombosis higher in survivors than in non-survivors. The operative findings and their relationship with mortality are listed in *Table 5*. Nine patients developed enterocutaneous postoperative fistulae and 10 required reoperation because of infection or the decision to undertake a planned second-look procedure. None of the relaparotomies proved to be negative

Table 2 *Clinical and biochemical parameters in 83 patients with massive mesenteric infarction. A comparison between resected* (n = *44*) *and non-resected* (n = *39*) *patients*

	Resected patients		Non-resected patients	
	Mean ± s.d.	%	Mean ± s.d.	%
Age (years)	64·1 ± 11		71·0 ± 11*	
Male sex		66		61
Risk factors				
Ischaemic heart disease		18		23
Valvular heart disease		25		10
Arrhythmia		36		23
Other features of atherosclerosis		32		49
Respiratory diseases		25		13
Signs and symptoms				
Peritonitis		57		56
Bloody diarrhoea		23		23
Shock		32		36
Delay of treatment (h)	60·9 ± 71		72·1 ± 108	
Temperature (°C)	36·5 ± 0·8		36·5 ± 0·8	
Heart rate (beats/min)	103 ± 27		107 ± 26	
Abdominal films				
Mild ileus		29		19
Severe ileus		48		63
Laboratory tests				
BUN (mg/100 ml)	69·3 ± 52		52·8 ± 42	
Haematocrit (%)	44·8 ± 9		47·2 ± 8	
Leucocyte count ($\times 10^9$/l)	16·6 ± 0·1		17·2 ± 0·1	
Venous blood pH	7·36 ± 0·1		7·31 ± 0·1	
Aetiology				
Arterial thrombosis		48		67
Venous thrombosis		22		17
Arterial embolism		17		17
Non-occlusive ischaemia		13		0
Non-involved bowel (cm)	60·7 ± 40		54·4 ± 112**	

None of the observed differences were statistically significant except *$P = 0·006$, **$P < 0·02$ (information on non-resected patients available in only 9 patients); BUN, blood urea nitrogen

Table 3 *Age, sex and risk factors in 44 patients undergoing massive bowel resection because of mesenteric infarction*

	Whole series		Survivors		Non-survivors	
	Mean ± s.d.	*n* (%)	Mean ± s d	%	Mean ± s.d.	%
Age (years)	64·1 ± 11		62·8 ± 10		65·7 ± 12	
Male sex		29 (66)		63		70
Risk factors						
Ischaemic heart disease		8 (18)		25		10
Valvular heart disease		11 (25)		25		25
Arrhythmia		16 (36)		37		35
Other features of atherosclerosis		14 (32)		21		45
Respiratory diseases		11 (25)		25		25

None of the observed differences are statistically significant

Table 4 *Aetiology, clinical features and laboratory tests in 44 patients undergoing massive bowel resection because of mesenteric infarction*

	Whole series		Survivors		Non-survivors	
	Mean ± s d.	*n*(%)	Mean ± s.d	%	Mean ± s.d.	%
Signs of peritonitis		25 (57)		54		60
Bloody diarrhoea		10 (23)		30		15
Shock		14 (32)		25		40
Treatment delay (h)	61 ± 71		74 ± 90		43 ± 28	
Temperature (°C)	36 5 ± 0 8		36·7 ± 0 6		36·1 ± 0·8*	
Heart rate (beats/min)	103 ± 27		108 ± 30		95 ± 21	
BUN (mg/100 ml)	69 ± 52		54 ± 34		99 ± 69	
Haematocrit (%)	45 ± 9		42 ± 5		46 ± 13	
Leucocyte count (10^9/l)	16·6 ± 7		15 5 ± 6		18·8 ± 9	
Venous blood pH	7·36 ± 0 1		7·38 ± 0·08		7·34 ± 0·1	
Aetiology						
Arterial thrombosis		11 (48)		27		67
Venous thrombosis		5 (22)		45		0
Arterial embolism		4 (17)		18		17
Non-occlusive ischaemia		3 (13)		9		17
Unknown		21				

None of the observed differences are statistically significant except * $P < 0\ 03$ survivors *versus* non-survivors; BUN, blood urea nitrogen

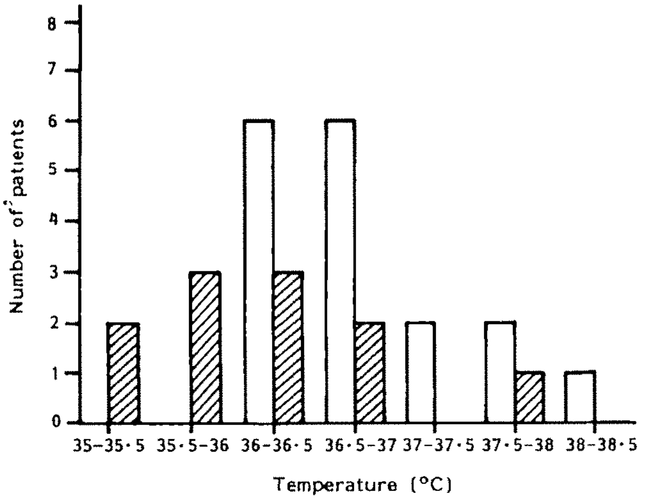

Figure 1 *Axillary temperature at admission in patients who died* (▨) *or survived* (☐) *after massive bowel resection*

although reoperation was significantly correlated with mortality. Early postoperative laboratory data are displayed in *Table 6*. Total plasma protein and albumin concentrations were significantly lower in patients who died after MBR. Discriminant stepwise analysis could be applied to 26 cases in which all the data were available. Pre-operative blood urea nitrogen levels, previous symptoms of atherosclerosis and postoperative total plasma protein concentration all significantly influenced the prognosis after MBR.

Twenty patients died after MBR. Mean survival time for these patients was 15 ± 22 days (range 0–105 days). Nine died during the first week as a result of their poor general status and eleven from specific postoperative complications, mainly intractable intra-abdominal infection. Survivors had a mean hospital stay of 57 ± 37 days (range 14–150 days). In these patients total parenteral nutrition (TPN) had to be maintained for a mean of 34 days (*Figure 2*). Outpatient follow-up data were available for 20 of the 24 survivors (mean follow-up 2 years, range 4–96 months). Intestinal adaptation appeared to have been good to excellent in 15 (75 per cent) of the cases in that re-admission for metabolic and/or nutritional reasons was not necessary. On the other hand, five patients did poorly in that they required repeated hospital re-admissions for metabolic and nutritional problems.

Discussion

Few large carefully documented series of massive mesenteric infarction have been reported. Although retrospectively reviewed, our experience has allowed us to clarify some ill-defined features of this disease. As reported by most authors, the peak incidence of mesenteric infarction occurs in the sixth or seventh decades of life[1,2,4,12]. In some series[2,5,13] both sexes were similarly involved, but in our experience and in that of other European studies[4,12,14] infarction was more common in males, a fact which could also be related to the high incidence of

Table 5 *Operative findings, procedures and postoperative clinical data in 44 patients undergoing massive bowel resection for mesenteric infarction*

	Whole series		Survivors		Non-survivors	
	Mean±s.d.	*n* (%)	Mean±s.d.	%	Mean±s.d.	%
Remaining small bowel (cm)	60±40		64±37		57±44	
Bowel perforation		4 (9)		4		15
Ileocaecal valve preserved		11 (25)		25		26
Enterostomy		5 (11)		5		21
Enterocutaneous postoperative fistula		9 (20)		12		30
Reoperation		10 (23)		8		40*

None of the observed differences are statistically significant except *$P<0·03$

Table 6 *Early postoperative laboratory data in 44 patients undergoing massive bowel resection for mesenteric infarction*

	Whole series	Survivors	Non-survivors	
	Mean±s.d.	Mean±s.d.	Mean±s.d.	Significance
Plasma proteins (g/l)	54±9	57±8	46±10	<0·0005
Albumin (g/l)	26±4	27±4	22±4	<0·02
Creatinine (mg/100 ml)	1·8±1·5	1·8±1·7	1·8±0·9	n.s.
BUN (mg/100 ml)	62±43	62±36	62±54	n.s.
Haematocrit (%)	38±6	38±5	40±7	n.s.

BUN, blood urea nitrogen; n.s., not significant

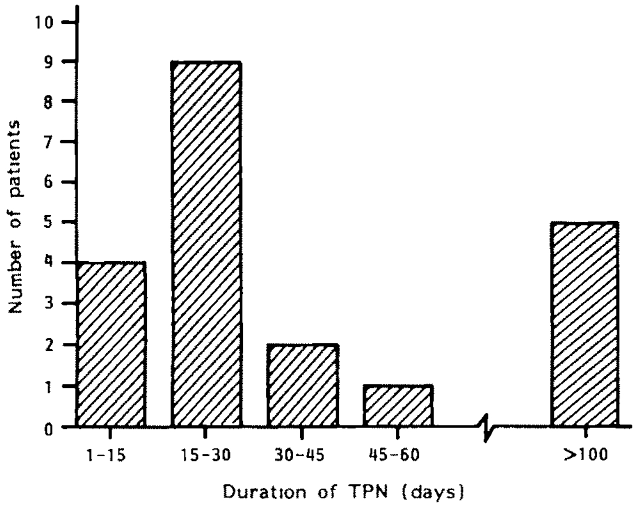

Figure 2 *Total parenteral nutrition (TPN) requirements in patients surviving massive bowel resection for mesenteric infarction*

superior mesenteric artery thrombosis in our patient population. The high incidence of previous signs or symptoms of atherosclerosis in our series was particularly striking and had a major influence on mortality.

Axillary temperature has not been carefully evaluated in patients with mesenteric infarction. Boley *et al.*[7] reported temperatures higher than 38°C in 38 per cent of their patients and Andersson *et al.*[5] found a slight increase in mean temperature (37·7°C). In our series fever was present in only 19 per cent of cases and hypothermia was recorded in 26 per cent. The lack of correlation between hypothermia and the presence of shock indicates that low body temperature *per se* may be a common finding in mesenteric infarction. Furthermore, as illustrated in *Figure 1*, body temperature was related to outcome. More studies are needed to confirm these findings that may indicate a general failure of physiological and metabolic adaptation to severe stress in this population of old and often malnourished patients.

The association of a normal or increased haematocrit with a raised blood urea nitrogen and metabolic acidosis underlines the importance of fluid loss in this condition. This has also been noted recently by Abdu *et al.*[15] in patients with venous thrombosis and can be due both to previous dehydration (water deficit being a predisposing factor for arterial or vein thrombosis) and to a third-space syndrome caused by sequestration of extracellular fluid in the intestinal lumen. Whatever the cause, aggressive fluid replacement seems to be of the utmost importance in the perioperative resuscitation of patients with mesenteric infarction.

It has been postulated that an aggressive vascular surgical approach could improve the overall outcome of mesenteric infarction. We acknowledge that, in our experience, most patients have not had the chance to undergo this kind of surgery, which aims to preserve a greater length of small bowel. In general, patients with superior mesenteric arterial thrombosis are in a poor general condition, with advanced intestinal ischaemia at the time of laparotomy, and have little chance of survival. Patients with mesenteric vein thrombosis are not candidates for vascular surgery and as a subgroup have done well after MBR. Favourable results from vascular techniques have been obtained only in a few cases of arterial embolism[1,6], a relatively rare cause of mesenteric infarction in our country[4,14] when compared with series reported in the American literature which show a higher proportion of patients with emboli and venous thrombosis[13]. It is a matter of debate whether routine use of angiographic techniques (not available during the period covered by our study) would have helped in the early diagnosis and treatment of these patients[16]. Frustrating results despite an aggressive vascular surgical approach have been reported by Ottinger[1].

There is controversy about when MBR should be carried out in patients with extensive bowel necrosis. In our retrospective analysis, age was the only factor that appeared to have influenced the surgeon's choice. Other indicators of severity of disease such as shock, bowel perforation, length of involved bowel or degree of renal failure were not taken into account. A survival rate superior to 50 per cent after MBR can be considered acceptable, although no recent data are available in the English literature in large series of patients having MBR for bowel infarction. Ottinger[1] reported a 25 per cent survival rate in patients with arterial occlusion undergoing resection without any associated vascular procedure. In our series, prognosis after MBR was not correlated with indicators of severity of the disease itself but with general physiological variables such as pre-operative renal function, temperature and nutrition. No patient undergoing MBR for venous thrombosis died and this underlines once more the better prognosis of this condition, which commonly has a more protracted course.

Oral refeeding was resumed as early as possible after MBR (once the diarrhoea could be controlled) and postoperative intestinal adaptation appeared to have been good in the majority of the 24 survivors, despite the fact that only one-third had preservation of the ileocaecal valve. Only five of those patients required postoperative TPN for more than 2 months or needed repeated hospitalization because of metabolic derangement and these patients were candidates for home TPN, which became available in Barcelona in 1985, after completion of this study. We now feel that patients requiring intravenous feeding for more than 2 months after MBR for bowel ischaemia should be considered candidates for home TPN. At variance with the experience of the Montpellier group[17], we have not observed recovery of intestinal function after this period.

In summary, our experience indicates that mesenteric infarction continues to be an abdominal catastrophe with an overall mortality rate of 71 per cent. The clinical picture is that of abdominal pain and severe fluid sequestration with poor peripheral perfusion and, commonly, hypothermia. In our hands, extensive bowel resection has resulted in a 54 per cent survival rate, the best prospect of survival having been obtained in patients without previous symptoms of atherosclerosis, relatively good physiological adaptation to the low flow state during the pre-operative period, and with acceptable postoperative visceral protein status.

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Errors in manuscripts

The Editorial Staff of the *British Journal of Surgery* are encountering increasing problems with authors' errors in manuscripts submitted for publication. Errors are found frequently in the calculation of percentages and commonly there are discrepancies within the article as far as numbers of patients are concerned. Other common problems include inconsistencies between the text and the abstract, failure to use SI units, errors in the terminology used to describe drugs and surgical materials, and major errors in the use of references. On numerous occasions the editorial staff have encountered difficulty at proof stage when attempting to resolve these problems with authors and it has emerged that not all authors are fully conversant with the material submitted. It must be emphasized that problems such as those listed above frequently delay publication of material in the Journal and may indeed jeopardize the acceptance of articles.

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Continuous enteral nutrition during the early adaptive stage of the short bowel syndrome

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Sixty-two patients with the short bowel syndrome (30–150 cm) were managed by continuous enteral nutrition (CEN) in the early adaptive phase. In all, 82 per cent were referrals from other units and 85 per cent of referrals had failure of one or more organ systems on admission. There were intra-abdominal abscesses in 41 per cent of patients and 37 per cent had an enterocutaneous fistula. The diet included polysaccharides, medium chain triglycerides and protein hydrolysates, mixed with a high-viscosity tapioca suspension. An elemental diet was used initially in 15 per cent of patients. Thirty-three patients had an interruption of the gastrointestinal tract by a temporary enterostomy. Chyme was re-infused into the distal intestine in 20 cases. 'Zero-time' was taken as the time of operation or, for referred patients treated conservatively, the date of admission. CEN was commenced at a mean of 14 days from zero-time. Total parenteral nutrition could be discontinued at a mean of 36 days and exclusive oral alimentation was resumed at a mean of 87 days. Patients with small bowel longer than 80 cm attained enteral autonomy earlier than patients with a shorter length. Mean faecal volume did not increase following institution of CEN, suggesting tolerance to the high-viscosity diet. In cases with re-infusion of enteric content, the distal circuit (length of distal small intestine 46 cm) was able to absorb 70 per cent of the volume re-infused (mean volume 2700 ml). Body weight and nutritional markers increased significantly during the course of CEN. This study suggests that enteral autonomy can be attained early in the short bowel syndrome, even under challenging conditions. Elemental formulae do not appear to offer a benefit over polymeric diets.

Keywords: Enteral nutrition, short bowel syndrome, adaptation

Massive bowel resection is required mainly in patients with mesenteric infarction, Crohn's disease, and septic complications following gastrointestinal surgery[1]. The first postoperative weeks may be associated with intra-abdominal sepsis, enterocutaneous fistulae, and organ system failure.

In the digestive intensive care unit at Hôpital Saint-Antoine (HSA), a referral centre for abdominal septic conditions, an attempt has been made in these patients to replace total parenteral nutrition (TPN) as soon as possible by continuous enteral nutrition (CEN). We report our experience with 62 short bowel patients with abdominal complications and/or organ system failure managed with CEN during the early adaptive phase following resection. The purpose of this study was to ascertain the natural history of the early phase of the short bowel syndrome and to assess the value of CEN as the main nutritional support during this period.

Patients and methods

Patients

Sixty-two patients with 30–150 cm of small bowel remaining after resection (measured at laparotomy along the antimesenteric border) have been managed in the surgical intensive care unit during the period 1975–85.

The study group is comprised of 37 men and 25 women, with a mean age of 55 years (range 8–82), who were the survivors of a group of 82 patients seen with a short bowel syndrome. The 20 who died early after admission did so from septic complications before any attempt at management by enteral nutrition. The indications for resection in the 62 surviving patients were: mesenteric infarction 28, intestinal obstruction 17, postoperative peritonitis 15, extensive Crohn's disease of the small bowel 2.

Eleven patients (18 per cent) underwent the initial surgery at our institution. Fifty-one patients (82 per cent) were referred from other institutions after one or more laparotomies. Thirty-six patients had undergone an extensive bowel resection before admission, the median time between resection and admission being 38 days (range 2–90). All referred patients had some abdominal complication on admission (intra-abdominal abscess 26, enterocutaneous fistulae 24, intestinal necrosis 11, abdominal wall dehiscence 11, intestinal obstruction 9) The general status of those patients was evaluated in terms of seven severity factors (*Table 1*). The mean severity score per patient was 1·8 No patient had received enteral alimentation between the initial surgery and

Table 1 *Severity factors in 51 referred patients*

Factors	*n*
Septicaemia (clinical signs and positive blood cultures)	37
Renal failure (serum creatinine >250 μmol/l)	15
Malnutrition (>20 per cent weight loss)	13
Adult respiratory distress syndrome (mechanical ventilation required for a minimum of 5 days)	10
Hepatic failure (serum bilirubin >90 μmol/l, or transaminases >3 × maximal value)	6
Thrombo-embolism (deep vein thrombosis, pulmonary embolism)	5
Shock (mean arterial blood pressure <60 mmHg)	4

Mean number of factors per patient 1 8

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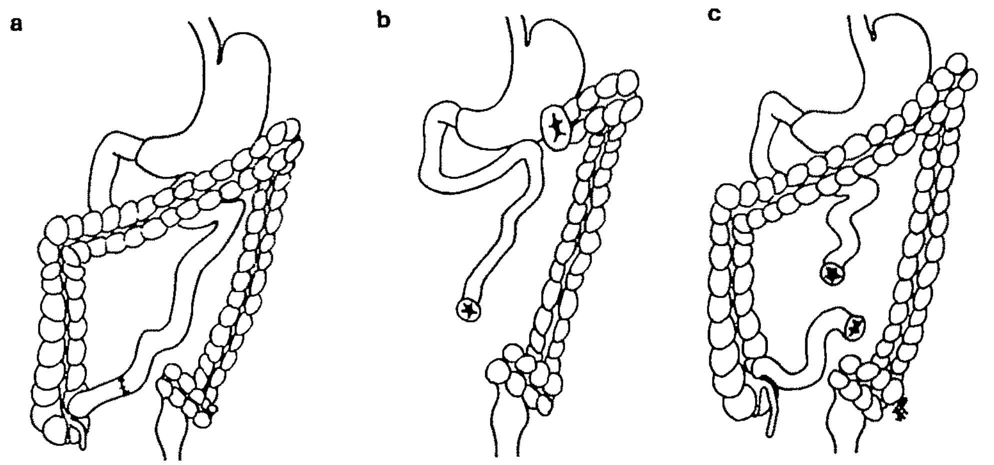

Figure 1 *Condition of the gastrointestinal tract at zero-time* **a** *Uninterrupted circuit,* **b** *terminal jejunostomy and colonic fistula,* **c** *terminal jejunostomy and ileal mucous fistula*

admission to HSA, because of persisting intra-abdominal complications throughout this period.

Operations performed at HSA Ten patients among the referrals were managed conservatively Thus a total of 52 patients were operated upon at HSA Extensive resection of the small bowel was undertaken in 26 patients. A temporary enterostomy was performed in 27 cases.

After surgery at HSA, the patients were divided into three categories according to their digestive status: uninterrupted gastrointestinal tract ($n = 29$), terminal jejunostomy and colonic mucous fistula ($n = 13$), interruption of the small bowel with jejunostomy and ileal mucous fistula ($n = 20$). Patients in the last group had re-infusion of the enteric content from the proximal stoma into the distal small bowel using a specially designed infusion pump[2]. Therefore the length of functional small bowel was equal to the total length of remaining small intestine in all patients. The length of functional small bowel ranged from 30 cm to 150 cm with an average of 87·4 cm. Patients were divided into two groups according to the length of functional small bowel. group 1, >80 cm of functional small bowel (mean length 119 cm, $n = 41$); group 2, <80 cm of functional small bowel (mean length 54·5 cm, $n = 21$).

Methods

The day of reference for the tabulation of TPN, intravenous perfusion, and CEN, defined as 'zero-time', was taken either as the day of operation for patients operated on after admission, or the date of admission for those receiving conservative treatment. With regard to faecal volume and the value of the nutritional markers, the starting day was the day of onset of CEN

Nutritional support. All patients received TPN in the immediate postoperative period CEN was commenced as soon as possible, that is, on average, 14 days after zero-time. In 85 per cent of cases, the nutritive diet was composed of the following ingredients

> *Carbohydrate.* Oligosides plus polyosides (Caloreen®, Sopharga Laboratories, 5 rue Bellini F 92806 Puteaux, France). Glucose 1·5 per cent, maltose 5·3 per cent, oligosides 52 6 per cent, polyosides 40 6 per cent; 4 kcal/g, osmolarity of a 10 per cent solution 90 mosmol/l.
>
> *Fat.* Medium chain triglycerides and grape seed oil (Liprocil®, Sopharga Laboratories) Medium chain triglycerides 80 per cent, grape seed oil 20 per cent, supplemented with vitamins A, B2, E, 9 kcal/ml, concentration of linoleic acid 14·7 per cent.
>
> *Protein.* Milk proteins (Alburone®, Sopharga Laboratories). Casein, lactalbumin, and lactoglobulin hydrolysate; 3·7 kcal/g; osmolarity of a 10 per cent solution 77 mosmol/l.

In all, 15 per cent of the patients received their protein supply as amino-acids or oligopeptides (Reabilan®, Sopharga Laboratories). Care was taken to keep osmolarity low (below 380 mosmol/l) and, therefore, electrolytes were supplied either intravenously or through an excluded large bowel segment until intestinal adaptation allowed provision of electrolytes in the diet

A viscous additive (tapioca solution or modified indian corn starch, Amidon Visco®, Gallia Laboratoires, F 92203 Levallois, France) was mixed with the nutritive diet in order to attain a high viscosity. The average viscosity of the final solution was 10 poises (i.e. 8 times the viscosity of glycerine at 37°C).

Table 2 *Physical characteristics of the enteral diet: caloric distribution*

Characteristic	Value
Caloric concentration (mean)	1 05 kcal/ml
Osmolarity (range)	250–350 mosmol/l
Calorie repartition	
Carbohydrate (mean ± s d.)	62 ± 11%
Fat (mean ± s.d.)	23 ± 7%
Protein (mean ± s.d.)	15 ± 3%
Mean daily calorie intake at full strength	3230 kcal
Mean daily calorie intake per kilogram body weight	55·4 kcal
Mean daily nitrogen intake	17 g
Nitrogen: calorie ratio (mean)	1:188

The distribution of calories and other characteristics of the diet are shown in *Table 2.*

The infused dietary volume was 500 ml on the first day and was slowly increased until the maximal infusion rate was reached, this was reached at a mean of 14 days after beginning CEN. The site of infusion was the stomach in 55 cases (N-G tube 31, Witzel gastrostomy 24) and the jejunum in 7 cases. The infusion tubes used were size 14 French soft elastomer tubes in the case of gastric infusion, and size 12 French for jejunostomy infusion (Vygon Laboratoires, F 95440 Ecouen, France) Gastrostomy was performed as a definitive procedure with a view to long-term CEN in the 11 patients undergoing primary operation in HSA and in 13 referred patients. A jejunostomy was constructed in seven patients with extensive bowel resection and acute disease of the upper gastrointestinal tract at the time of admission. Nasogastric tubes were used for conservative management and in patients where gastrostomy was technically difficult to perform on reoperation. Patients were given loperamide (4–8 mg/day) when considered appropriate clinically.

Re-infusion of chyme, when performed, was commenced at a mean of 8 4 days after the onset of CEN; the percentage of chyme re-infused was progressively increased from 25 to 100 per cent over a mean period of 6 days, a 100 per cent re-infusion rate was reached at the time of full-strength CEN

A glucose/electrolyte solution was infused into the excluded colon in nine patients

Statistical analyses included the Student t test, for quantitative data, and the χ^2 test, for qualitative criteria Numerical values are expressed as the mean ± 2 s e.m.

The following variables were analysed: faecal volume, body weight (expressed as the percentage of difference from its value at onset of CEN), nutritional markers, serum transaminases and nitrogen balance (calculated according to the Kjeldahl technique)

Results were tabulated against the length of remaining small bowel, and the delay between small bowel resection and admission

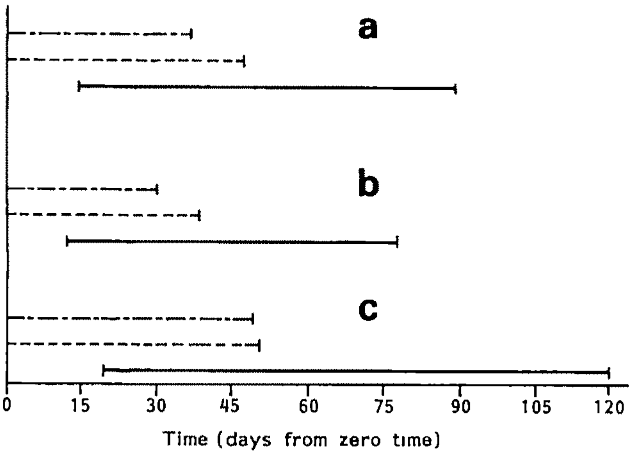

Figure 2 *Duration of total parenteral nutrition (— — —), intravenous perfusion (---), and continuous enteral nutrition (———)* **a** *Overall series;* **b** *group 1, functional small bowel >80 cm;* **c** *group 2, functional small bowel ≤80 cm*

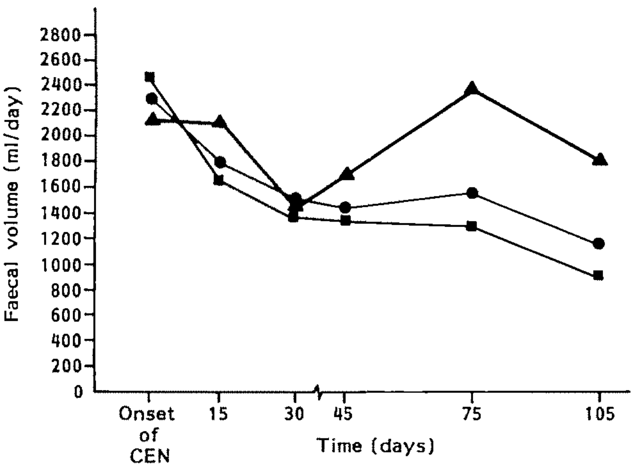

Figure 3 *Changes in mean faecal volume during continuous enteral nutrition.* ●, *Overall series,* ■, *group 1, functional small bowel >80 cm,* ▲, *group 2, functional small bowel ≤80 cm*

Results

CEN was commenced at a mean of 14 days from zero-time; earlier in group 1 (11 days) than in group 2 (19 days, $P<0\cdot05$). The mean duration of CEN, until exclusive oral alimentation could be resumed, was 75 days and was significantly shorter in group 1 (66 *versus* 101 days, $P<0\cdot0001$; *Figure 2*). The mean daily enteral caloric intake was 55 kcal/kg body weight, and was higher in group 1 (58 *versus* 45 kcal/kg, $P<0\cdot001$). Enteric content re-infusion was continued until restoration of intestinal continuity; the mean duration was 73 days.

TPN could be discontinued in all cases at a mean of 35·8 days from zero-time. Duration of TPN was longer in group 2 (49 *versus* 29 days, $P<0\cdot001$).

Intravenous infusion of water and electrolytes was discontinued at a mean of 46 days after zero-time (37 days for group 1 *versus* 50 days for group 2, $P<0\cdot05$).

Complications possibly related to TPN occurred in 24 patients (39 per cent). Septicaemia, defined by fever, positive blood culture and positive culture of the catheter for the same microbial strain, was observed in 22 patients; venous thrombosis occurred in 2 patients; and pneumothorax in 3.

Outcome

A total of 11 patients died after 30 days from admission (septicaemia 3, hepatic failure 3, uncontrolled sepsis 3, upper gastrointestinal tract haemorrhage 1, cancer 1). The remaining 51 patients resumed oral alimentation at a mean of 42 days after zero-time. Oral intake was progressively increased to become the sole nutritional support in 50 patients, at a mean of 87 days from zero-time. One patient did not do well with CEN and we had to resort to home TPN. Exclusive oral alimentation was reached at 76 days in group 1 *versus* 119 days in group 2 ($P<0\cdot001$).

Changes in faecal volume

Mean faecal volume was 2400 ml/day at the onset of CEN. Thereafter, it progressively decreased to 1800 ml as CEN reached full strength, and to 1400 ml after 45 days (*Figure 3*).

The absorptive capacity of the distal small bowel, in the case of re-infusion, is illustrated by *Figure 4*. The volume issuing from the proximal stoma ranged from 2500 to 3200 ml, the mean length of proximal bowel being 66 cm. This volume was all re-infused. The volume of effluent from the distal bowel ranged from 700 to 1200 ml, the mean length of distal intestine being 46 cm. *Figure 4* also shows that faecal volume flowing from the proximal stoma under CEN did not rise above initial values.

Nutritional markers

Body weight decreased for approximately 1 month, and then increased to reach, after 3 months, its maximal value of 5·5 per cent over the initial weight ($P<0\cdot001$ compared with initial weight, *Figure 5*).

Serum cholesterol rose by 33 per cent over 2 months (from 2·5±0·4 to 3·4±0·5 mmol/l, $P<0\cdot05$), and remained stable thereafter. Serum triglyceride increased during the first month of CEN (i.e. under the combination of CEN and TPN) and remained stable under exclusive enteral support. Serum albumin and serum protein were both increased significantly ($P<0\cdot05$) after 1 month of a combination of CEN and TPN, and then showed only minor changes (*Figure 5*).

The values of haematocrit, calcium, phosphate, blood urea and electrolytes, and creatinine remained within the normal range. Serum transaminases changed as follows: aspartate aminotransferase remained within the normal values whereas alanine aminotransferase was above the normal range in 20 per cent of patients at onset of CEN. Thereafter, this

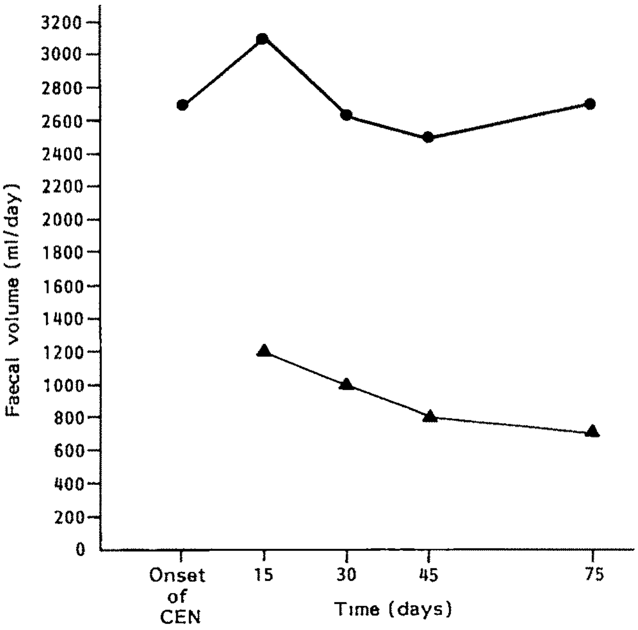

Figure 4 *Patients with re-infusion of enteric content.* ●, *Faecal volume flowing from the proximal stoma (length of proximal bowel 66±17 cm) and re-infused in the distal circuit,* ▲, *faecal volume flowing from the distal circuit (length of distal bowel 46±16 cm)*

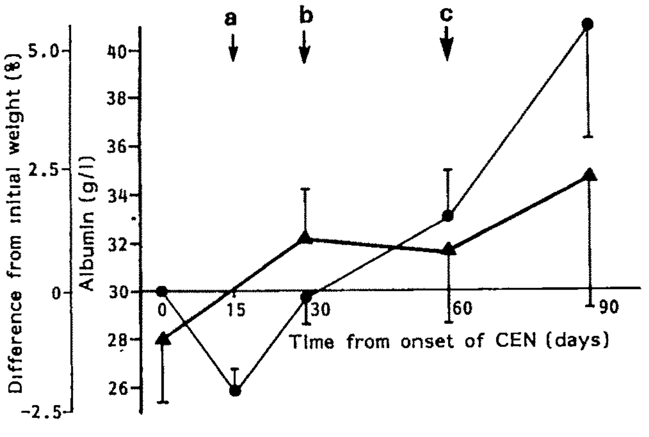

Figure 5 *Changes in mean body weight and serum albumin during continuous enteral nutrition (CEN). Body weight is expressed as a percentage of the difference from initial weight, i.e. weight at onset of CEN.* ●, *Body weight;* ▲, *albumin (mean ± 2 s.e.m.).* **a** *Indicates end of total parenteral nutrition,* **b** *end of intravenous perfusion,* **c** *end of CEN*

percentage increased to 33, 61 and 48 per cent at 15, 30 and 60 days respectively. In all patients, alanine aminotransferase remained below three times the maximal value; 90 days after onset of CEN, alanine aminotransferase returned to within the normal range.

Nitrogen balance was routinely evaluated in 25 patients in the period 1980–85. In all cases the data were collected during exclusive enteral nutritional support by CEN. Nitrogen balance was positive in 23 cases (92 per cent). Mean values of nitrogen balance were +3·2 g in the first month from zero-time, +7·8 g in the second month, and +6·4 g in the third month.

Effect of functional small bowel length

Group 1 and group 2 have been compared with regard to faecal volume, body weight and nutritional markers. Mean faecal volume was greater in group 2, but only at a late period (*Figure 3*). Body weight remained below basal value in group 2 while in group 1 it decreased in the initial phase, reached basal value at 30 days, and finally progressed up to 8 per cent over basal value at 90 days. There was no significant difference in the nutritional markers between the two groups.

Effect of the delay between small bowel resection and admission

The study group could be divided in two categories according to the time of small bowel resection: 36 patients had undergone resection at HSA or within 30 days before admission, while in 26 patients the delay between resection and admission was >30 days. In the latter group, CEN could be undertaken earlier (12 days from zero-time *versus* 17 days; difference not significant) but enteral autonomy was attained slightly later than in the former group. There was no difference with regard to mean faecal volume and nutritional markers.

Long-term results

Forty-seven patients were evaluable for long-term functional results while four were lost to follow-up; 62 per cent had 'excellent' or 'good' nutritional status (*Table 3*, 70 per cent of the evaluable patients in group 1 *versus* 47 per cent of those evaluable in group 2).

Body weight remained below the pre-operative value in 80 per cent of the patients, the average difference being 9·2 per cent (range 5–20). In group 1 weight attained its pre-operative value in 9 patients and remained below in 20 (8·7 per cent average weight loss). In all patients in group 2 weight remained below the pre-operative value (11·1 per cent mean weight loss).

Discussion

Conventional guidelines for the management of the short bowel syndrome include nutritional support by TPN in the early stage, i.e. 2–6 months[1,3], and its gradual replacement by oral alimentation and dietary supplements. This may be achieved successfully in stable patients[3], but in those with organ system failure and intra-abdominal complications, prolonged TPN can constitute a major threat[4], as reflected in the high rate of catheter-related complications in our series. This high incidence of venous complications is because of the poor condition of our patients, in whom effective prevention of contamination may be difficult. The use of the central line for multiple purposes, the presence of a high output fistula or stoma, and the presence of purulent discharge from a surgical wound all play a major role in the infectious complications to which these patients are prone.

It should be emphasized that this series comprises a large proportion of critically ill cases, as all the referred patients had undergone extensive bowel resection and were admitted after failure of previous therapy in the primary institution. Many of them had venous thrombosis or catheter-related septicaemia before admission. An alternative to TPN is therefore advantageous in this group of short bowel patients. Results from this series show that, provided appropriate techniques are used, nutritional autonomy with exclusive enteral support can be attained early in short bowel patients, even under challenging circumstances.

Twenty-six patients had undergone small bowel resection more than 30 days before admission. All had persisting intra-abdominal complications and none had received enteral nutrition. It was not until reoperation at HSA that a stable clinical state could be attained. For these reasons, and in the light of previous clinical experience, we felt that these patients could be regarded as still being in the early adaptive stage of short bowel syndrome. The tabulation of data against the time between resection and admission supports this hypothesis.

These results also support several hypotheses suggested by previous clinical and animal studies. Intestinal adaptation after massive resection occurs within a short period[5], and enteral alimentation stimulates the adaptive changes after resection[6–9]. Additionally, it appears that complex diets stimulate adaptive changes more effectively than elemental formulae[10].

Faecal volume during enteral nutrition showed a progressive decrease despite a steady increase in the volume infused. The explanation for this may be threefold. Firstly, the faecal weight at the onset of CEN was remarkably high, possibly due to inflammatory changes in the gastrointestinal tract which diminish as enteral nutrition proceeds. Secondly, CEN is associated with slow gastrointestinal motility and a reduction in gastric emptying has been documented by cineradiography[11]. In addition, the intestinal myoelectrical pattern during CEN has been shown to be similar to that observed in the fasting state[12]. Prospective studies in ileostomy patients have shown that, for a given diet, transit time with CEN was two to three times longer

Table 3 *Long-term functional results*

Result	Total	Group 1	Group 2
'Excellent' (return to normal life, minor or no dietary restrictions, 2–3 bowel movements/day)	11	8	3
'Good' (part-time work, 3–6 bowel movements/day)	18	13	5
'Fair' (unable to work, severe dietary restrictions, 4–10 bowel movements/day)	17	8	9
Home parenteral nutrition	1	0	1
Lost to follow-up	4	3	1
Deceased	11	9	2
Total	62	41	21

than with bolus meals[13]. Thirdly, the viscous additive increases the viscosity of the diet 200 times, thus increasing the transit time and the absorptive ability of a short intestinal segment. This appears to be a major contribution to the management of patients with a short bowel, although viscous diets require large bore infusion tubes of at least 12 French diameter.

The presence of a temporary enterostomy allows evaluation of the absorptive capacity of a short segment of ileum (*Figure 4*). Our data confirm the great adaptive capacity reported for the ileum and colon[14].

Elemental diets do not appear to be required in the management of the short bowel syndrome, even at an early stage. The theoretical advantage of providing readily absorbable nutrients is offset by the high osmolarity of these solutions, and our clinical experience has revealed that osmolarity is critical in the enteral support of short gut patients. MacIntyre[15], in a comparative study, showed that an elemental diet had no benefit over a polymeric preparation in the short gut syndrome. An elemental diet was used only in 15 per cent of patients in this series, at the commencement of CEN. It was not suitable for the provision of a high calorie requirement due to excessive osmolarity and those patients were gradually weaned on to the polymeric diet.

The long-term results are beyond the scope of this study, but suffice it to say that all patients but one resumed oral alimentation on a long-term basis (*Table 3*). It should be emphasized that, although the data reported in this study are mean values, individual variations are important, particularly in relation to age, race, geographical origin, previous condition and past history.

In conclusion, high-viscosity CEN is a viable alternative to TPN in the early adaptive phase of short bowel syndrome. It allows early withdrawal of intracaval catheters in patients at high risk of venous complications. Early enteral support stimulates the adaptive changes in the residual small intestine, allowing oral alimentation to be resumed after a short period of time. Even in the early stages, polymeric diets appear to be associated with a good tolerance and elemental formulae are required only in a small percentage of cases at the beginning of a course of CEN.

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Plain abdominal radiographs and acute abdominal pain

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The records of all (5080) patients presenting to a district general hospital with acute abdominal pain over a 4-year period were examined. The contribution of abdominal radiographs to the assessment of patients with suspected appendicitis, urinary tract infection, and non-specific abdominal pain was evaluated, these conditions accounting for 48 per cent of patients with abdominal pain and 32 per cent of those with abdominal radiographs. Any positive information from these radiographs was less likely to be helpful than incidental or inconsistent (and hence potentially misleading). Because of this high 'false positive' rate it is suggested that if the initial diagnosis is suspected appendicitis, urinary tract infection, or non-specific abdominal pain, there is little value in the routine use of abdominal radiographs.

Keywords: Acute abdomen appendicitis, radiography, urinary tract infections

The rational use of investigations depends on knowing how the results will influence the diagnostic process. In the assessment of patients with acute abdominal pain the indiscriminate use of plain abdominal radiographs is likely to be wasteful in terms of many normal results, and possibly misleading in showing abnormalities which are coincidental. Although it has been advocated that an abdominal radiograph should be part of the routine assessment of patients with acute abdominal pain[1] there are many occasions when it is unlikely to provide any useful information. We have examined the results from three diagnostic groups of patients where it was felt abdominal radiographs would have little to contribute, namely suspected appendicitis, urinary tract infection, and non-specific abdominal pain.

Patients and methods

Data were collected on 5080 patients with acute abdominal pain. This comprises all such patients referred to a district general hospital over the 4-year period 1980–1983 but excludes those with trauma. Of these patients 45 per cent had a plain abdominal radiograph performed. A structured record was used routinely in conjunction with computer–aided diagnosis[2], and the resulting computer records form the basis for this study. This record contains the initial diagnosis and the final diagnosis. The 'initial diagnosis' is made by the junior medical staff in the accident and emergency department after seeing the patient, but before arranging any investigations. The final diagnosis was made by a senior consultant (A.A G.) after consideration of all the clinical features, investigations, operative and pathological findings When there was still doubt after such consideration a 'no diagnosis' category was assigned In 3·4 per cent of the patients studied no final diagnosis was reached.

The records were examined according to the initial diagnosis as it was on this basis that the first investigations were selected. Three diagnostic categories were selected for study as conditions where it was thought that abdominal radiographs were unlikely to be helpful, namely suspected appendicitis, urinary tract infection, and non-specific abdominal pain. These suspected diagnoses accounted for 48 per cent of all patients with acute abdominal pain (2442/5080), and 32 per cent of all those having plain abdominal radiographs (739/2310)

The radiographs were all reported by one of three consultant radiologists, and those showing any abnormality were regarded as positive. The number of positive radiographs in each group is shown in *Figure 1*. In addition to a supine view less than half of the subjects also had an erect view; it is now the agreed policy of the departments of radiology and surgery to request a supine view only when radiography is indicated. Any information from chest radiographs was disregarded for the purpose of this study.

Positive radiographs were further classified as being 'helpful', 'inconsistent', or 'incidental'. Helpful radiographs were those showing an abnormality consistent with the final diagnosis, e g renal stones where the final diagnosis was renal colic, or signs of intestinal obstruction where this was the final diagnosis. Incidental results were abnormalities, such as arthritis of the spine, which were clearly unrelated to the acute abdominal pain. Results which suggested a diagnosis which was not proved correct after full investigation and treatment were classified as inconsistent, e.g. gallstones or signs of intestinal obstruction where the final diagnosis was neither gallbladder disease nor intestinal obstruction. Some of these inconsistent results could be regarded as potentially misleading. As this is a retrospective study the reports represent a radiologist's opinion rather than the application of strictly defined criteria, and some radiological diagnoses can be made with more certainty than others.

Results

Suspected appendicitis

Of the 808 patients with suspected appendicitis 155 (19 per cent) had an abdominal radiograph taken. More than 30 doctors worked in the accident and emergency department during the study period and there was no specific policy on the selection of investigations. From a retrospective analysis of the case notes it was not usually apparent why an X–ray examination had been requested Most of these radiographs (123/155, 79 per cent) were reported by the radiologists as normal. Thirty-two radiographs (21 per cent) showed positive features with the

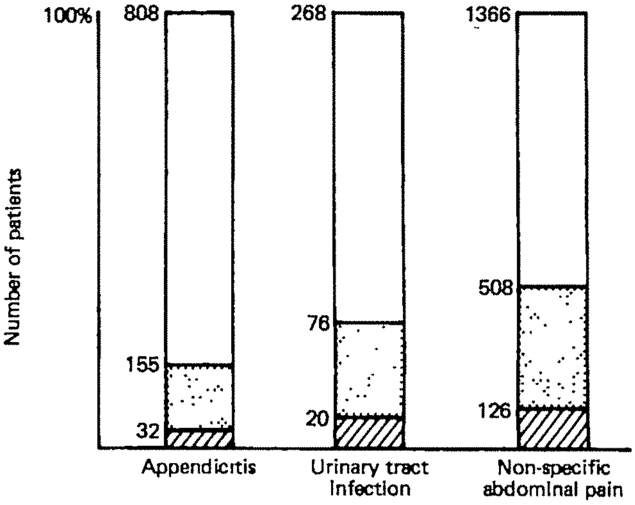

Figure 1 *Proportions of patients with positive and negative radiographs, □, no X-ray, □, negative X-ray; ▨, positive X-ray. The number of patients involved is shown*

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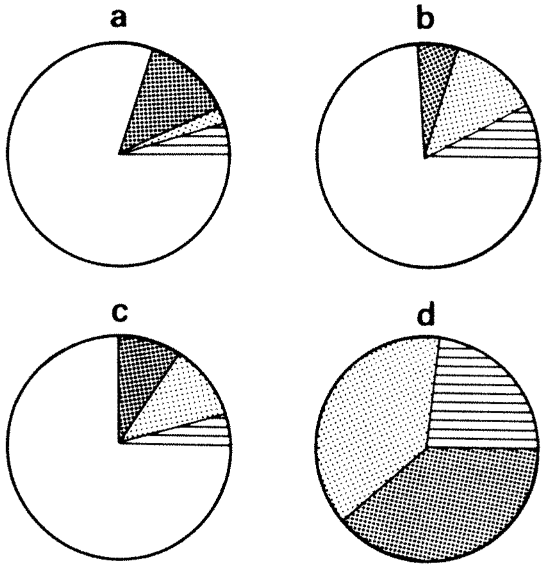

Figure 2 *Results of radiographs in each diagnostic group.* **a,** *Appendicitis;* **b,** *urinary tract infection;* **c,** *non-specific abdominal pain;* **d,** *combined results from all three diagnostic groups;* □, *negative;* ▩, *inconsistent;* ▨, *incidental;* ▤, *helpful*

following results. Two were helpful in suggesting another diagnosis which turned out to be correct (one perforation and one intestinal obstruction). Four had incidental features, such as arthritis of the spine. Eleven were inconsistent showing features which did not fit with the final diagnosis. Fifteen showed non-specific features consistent with appendicitis, such as local ileus, right iliac fossa mass and scoliosis, but the initial diagnosis of appendicitis was confirmed in only six, leaving nine with a final diagnosis unrelated to the radiographic abnormality, i.e. six helpful and nine inconsistent.

If the non-specific radiographic features are accepted as useful diagnostic pointers then there were 8 (2+6) helpful radiographs, but 20 (11+9) inconsistent radiographs some of which might have been misleading if accepted uncritically (*Figure 2*).

Suspected urinary tract infection

Of the 268 patients with suspected urinary tract infection, 28 per cent had a radiograph of which one in four showed some abnormality. Of these 20 radiographs 9 showed incidental findings. Seven were helpful in establishing the final diagnosis, e.g. showing intestinal obstruction or renal stones where these findings were confirmed as the cause of the abdominal pain. However, four were inconsistent, suggesting a diagnosis that was not confirmed, e.g. renal stones in a patient with a final diagnosis of diverticulitis (*Figure 2*).

Suspected non-specific abdominal pain

Of 1366 patients with an initial diagnosis of non-specific abdominal pain (NSAP) 508 (37 per cent) had a plain abdominal radiograph. Most of the radiographs (75 per cent) showed no abnormality. Of the 126 radiographs (25 per cent) which showed positive features, 57 gave incidental findings with no bearing on the immediate problem. The results of 27 radiographs were helpful in suggesting an alternative diagnosis which was proved to be correct, but 42 radiographs were inconsistent in suggesting a diagnosis which on retrospective analysis was incorrect (*Figure 2*).

When the results from the three diagnostic groups are combined, the inconsistent radiographs outnumber the helpful radiographs in a ratio of 3:2 and, while some of these could be reclassified as incidental if they were clearly unrelated to the clinical picture, in many instances they might provide potentially misleading information.

Discussion

Lee[1] has advocated that an abdominal radiograph should be a routine investigation for all patients with acute abdominal pain. However this conclusion was based on a selected group of 500 patients who required hospital admission. He found specific radiological features in 48 per cent of these patients, but in many instances these were non-specific signs, such as local ileus, that cannot be regarded as diagnostic. In our unselected series of more than 5000 consecutive patients (of whom 65 per cent were admitted) only 46 per cent had an abdominal radiograph of which 60 per cent were entirely normal. These figures are very close to those of Brewer *et al.*[3] who looked at 1000 consecutive cases of abdominal pain; 43 per cent of patients were X-rayed with 62 per cent of radiographs being normal. He found that in only 58 cases was positive information provided, but in no case was the diagnosis changed by the radiographic finding.

In a further series of 1780 X-ray examinations it was found that only 10 per cent showed some abnormality[4]. The authors conclude that if they had restricted radiographs to those with moderate/severe tenderness, suspected intestinal obstruction, renal colic, trauma, ischaemia, or gallbladder disease then 54 per cent of radiographs could have been avoided without missing any serious abnormalities. This more limited role of abdominal radiographs is also supported by Stower *et al.*[5] who judged whether diagnosis or management was affected by the abdominal radiograph in 50 consecutive cases. The radiographic results contributed to a change in diagnosis in only five patients, and a change in management in three. However, in another series of 100 radiographs[6] a management change resulted from 10 per cent of radiographs.

Where an abdominal radiograph is indicated the routine use of both erect and supine views has been questioned[6-8]. In the series of DeLacey *et al.*[8] 94 per cent of requests for erect radiographs were considered unnecessary, and in the series of Field *et al.*[7] the erect view did not lead to any changes in management. Although DeLacey *et al.*[8] consider that suspected intestinal obstruction is one of the few indications for an erect radiograph this view is challenged by Simpson *et al.*[9] who found that the erect film contributed little in addition to the supine film in 100 cases.

Unnecessary radiographs have costs in financial terms, in patient discomfort, and in gonadal irradiation. Our results suggest that for the 48 per cent of all patients with abdominal pain who are thought on initial assessment to have appendicitis, urinary tract infection, or non-specific abdominal pain, there is little value in taking a plain abdominal radiograph. In a department already conscious of the limited role of radiographs in the assessment of abdominal pain this policy could produce a further reduction of up to 32 per cent in the number of abdominal radiographs.

Acknowledgements

We thank Mrs Julie McLaren and Mrs Elizabeth Lumsden for maintaining the computer database and helping in extracting information. We are grateful to Mr D. A. D. Macleod and Mr I. W. J. Wallace for permission to include details of their patients in this study.

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Case report

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Duodenal erosion complicating an implanted hepatic arterial access device

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Selective infusion of cytotoxic agents via the hepatic artery has become an increasingly popular method of treating both primary and secondary liver cancer despite the need for operative siting of the catheter. The introduction of implantable drug delivery systems with silicone catheters has considerably minimized the incidence of catheter related complications[1,2]. We report an unusual complication following implantation of such a chemotherapeutic delivery system.

Case report

A 53-year-old woman with known hepatic metastases from a previously resected adenocarcinoma of the right colon was admitted with a 2–3-day history of general malaise, rigors and fever. Fifteen months previously a Port-a-cath (Pharmacia Nu Inc., Walpole, Massachusetts, USA) intra-arterial system had been surgically inserted, via the gastroduodenal artery, for hepatic arterial infusion of cytotoxic agents. Ligation of the right gastric artery and cholecystectomy were performed concomitantly. She underwent 12 cycles of chemotherapy without complication and this therapy was stopped 3 months before her present admission.

On examination, the patient's temperature was 39·5°C; she was not shocked. Clinical examination revealed no obvious source of infection. Blood cultures taken on admission grew *Bacteroides oralis* and *Citrobacter freundi*. There was a gradual clinical improvement and partial resolution of the pyrexia over several days with intravenous gentamicin, metronidazole and cefotaxime. In the absence of other obvious septic foci, it was decided to remove the presumed infected Port-a-cath system. Radiographic opacification was undertaken to determine patency of the hepatic artery. The catheter was patent but there was no flow in the hepatic artery and a communication with the first part of the duodenum was demonstrated (*Figure 1*). Comparison with previous abdominal X-rays showed no change in the position of the catheter. The catheter was removed under local anaesthesia without the development of a duodenal fistula and with complete resolution of the fever. *Enterobacter cloacae* and *Pseudomonas sp.* were isolated from fluid flushed from the catheter reservoir and *Acinetobacter sp.* from the catheter tip. The patient was discharged home 10 days after admission.

Discussion

Arterial thrombosis and catheter infection were frequent complications of intra-arterial chemotherapy when TEFLON® (Du Pont, UK) catheters were inserted percutaneously, with an incidence of 15–25 per cent and 5–20 per cent respectively[1,3,4]. These complications affect <3 per cent of patients when implantable devices with silicone catheters are used[1,2,5]. One case of pressure erosion of the gastrointestinal tract has been reported with a TEFLON catheter[4], but a literature search has failed to reveal such a complication with the more pliable silicone catheter. It is likely that pressure erosion of the duodenum preceded catheter infection in our patient and this is supported by the growth of several organisms of gut origin. The potential risk of gastrointestinal haemorrhage was not present because of the associated arterial thrombosis, which also allowed removal of the reservoir and catheter under local anaesthesia.

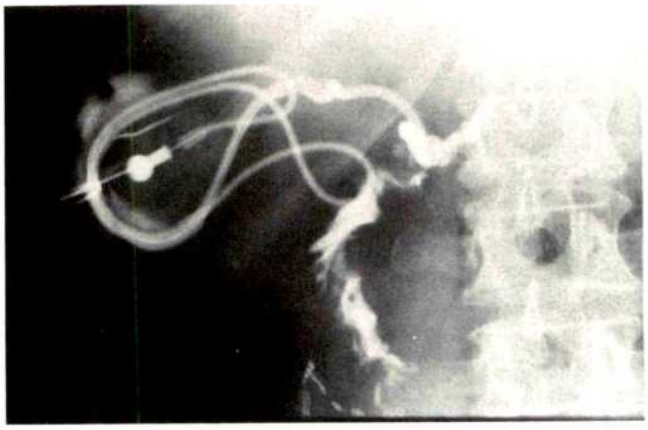

Figure 1 *Radiographic opacification of Port-a-cath showing contrast in and around the reservoir and catheter. A small collection, involving the distal 3 cm of the catheter, communicates with the first part of the duodenum. The first and second parts of the duodenum are outlined. Staples from the previous colonic anastomosis are also visible*

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Effect of epidural analgesia on postoperative insulin resistance as evaluated by insulin clamp technique

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The influence of epidural neural blockade on postoperative insulin resistance was studied using the euglycaemic insulin clamp technique. Eighteen patients undergoing elective upper abdominal surgery of moderate severity were allocated to two groups: group G patients underwent operation under general anaesthesia, and postoperative pain was relieved by systemic administration of analgesia; and group E patients received epidural analgesia during surgery and epidural morphine postoperatively. In each patient the euglycaemic insulin clamp test was performed twice: several days before surgery and on postoperative day 1. Peroperative catecholamine and cortisol responses were also measured to investigate possible endocrine mechanisms of the insulin resistance. Glucose disposal (M) decreased in both groups on postoperative day 1 at plasma insulin concentrations ranging from 1·2 to 10·0 milliunits ml^{-1}, resulting in the downward shift of dose-response curves. However, this downward shift was significantly smaller in group E than in group G patients. Urinary adrenaline excretion increased markedly on the day of operation in group G, but was significantly inhibited in group E. Urinary noradrenaline excretion increased mainly on postoperative day 1 in group G, but was significantly inhibited in group E. Plasma cortisol response was lower in group E than in group G during and shortly after operation, and was significantly inhibited in group E on postoperative day 1. These results indicate that insulin resistance after elective abdominal surgery is due to a postreceptor deficit in glucose utilization, as indicated by the downward shift of the dose-response curves. This disturbance in glucose metabolism was reduced by epidural analgesia, the results being associated with inhibited catecholamine and cortisol responses.

Keywords: Insulin resistance, euglycaemic insulin clamp, epidural analgesia

Glucose intolerance is an important metabolic change after major surgery. It is characterized by delayed glucose disposal in peripheral tissues from the blood despite elevated blood levels of insulin[1–5]. This indicates a decreased sensitivity to insulin, the so-called insulin resistance. It has been demonstrated that postoperative increase in the circulating levels of catabolic hormones is responsible for the impaired glucose utilization and insulin resistance[6,7]. Since epidural analgesia suppresses the endocrine response to surgery[8,9], the disturbance in postoperative glucose metabolism should also be modified. We have previously reported that prolonged epidural blockade after surgery resulted in lowered insulin/glucose ratios in the blood, which is an indirect indicator of insulin sensitivity[2]. However, direct evidence of mitigated insulin resistance has not been demonstrated.

Recently, the euglycaemic insulin clamp technique[10] has been used to assess the mechanisms involved in the pathogenesis of insulin resistance. The advantage of this technique is the ability to quantify the glucose disposal from the blood at a certain insulin level without changing the blood glucose concentration. By varying the plasma insulin levels, the dose-response curve of glucose disposal against plasma insulin concentrations can be constructed, by which the site of impaired insulin action can be defined[11–13].

In the present study the euglycaemic insulin clamp technique was used to demonstrate insulin resistance after elective abdominal surgery and to evaluate the effect of epidural analgesia in modifing the postoperative disturbance of glucose utilization. In addition, an attempt was made to assess the roles of catabolic hormones in postoperative insulin resistance.

Patients and methods

Eighteen patients undergoing elective upper abdominal surgery were studied. None took any medication before surgery, neither had they any hepatic, renal or metabolic illnesses. Patients with abnormal glucose tolerance, as determined by the 50 g oral glucose tolerance test performed before the study, were excluded. Informed consent was obtained from all patients.

Patients were allocated into two groups of nine. One group was operated on under general anaesthesia using halothane, nitrous oxide and oxygen (group G), and postoperative pain was relieved by intramuscular injections of pentazocine according to the patient's requests The other group was operated on under epidural analgesia using 0·5 per cent bupivacaine (group E), and postoperative pain was controlled by injections of 3 mg morphine in 5–10 ml saline through an epidural catheter every 12 h for 72 h. The detailed techniques of general anaesthesia and epidural analgesia have been previously reported[9] The characteristics of the two groups of patients are shown in *Table 1*. The two groups were comparable with regard to operative procedures, age, body height, body weight and magnitude of operation Group E patients were all pain-free postoperatively without any additional pain treatment. The schedule for intravenous infusion was identical in both groups; 10 ml kg^{-1} h^{-1} of lactated Ringer's solution was given during

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Table 1 *Characteristics of the patients*

	Group G	Group E
n	9	9
Sex: male/female	5/4	7/2
Operative procedure:		
Partial gastrectomy	4	4
Total gastrectomy	2	2
Cholecystectomy	3	3
Age (years)	55 ± 3	59 ± 5
Body height (cm)	157·1 ± 2·9	156·2 ± 2·1
Body weight (kg)	55·2 ± 2·8	51·4 ± 1·1
Operation time (min)	159 ± 20	183 ± 15
Blood loss (ml)	282 ± 60	362 ± 86

Figures are number of patients, mean values are group mean ± s.e.m. Group G, general anaesthesia group, group E, epidural analgesia group

operation, 1000 ml of 10 per cent glucose solution was given after operation, and 10 per cent glucose solution equivalent to 15 kcal kg^{-1} with added electrolyte solution was given on postoperative day 1. Only when blood loss was deemed excessive was citrated whole blood transfused during operation.

Euglycaemic insulin clamp study

The euglycaemic insulin clamp technique performed according to the method described by DeFronzo *et al.*[10], was carried out twice in each patient: several days before surgery and on postoperative day 1. The pre-operative study was performed after a 4–5 h fast, and the postoperative study after infusion of 500 ml of electrolyte solution only

Three indwelling catheters were placed in peripheral veins The first catheter was placed retrogradely in a dorsal hand vein and used for continuous blood withdrawal at the rate of 5 ml h^{-1}, which was introduced to an automatic glucose-measurement apparatus (Glucose Monitor, Kyoto Daiichi Kagaku Co. Ltd., Model GM 1320, Kyoto, Japan) to determine glucose concentrations every 2 min The second catheter was placed in an antecubital vein and connected to two infusion pumps via a Y adaptor in order to infuse glucose and insulin solutions The third catheter, placed in a wrist vein, was used for sampling blood to determine plasma insulin concentrations Both the hand and the wrist were kept in a heating chamber in order to obtain arterialized venous blood[14]. Between 30 and 60 min after venepuncture, basal measurements of blood glucose and insulin were made.

After the measurement of baseline glucose level, a 10 min priming infusion of crystalline porcine insulin was given according to the protocol described by DeFronzo *et al*[10], followed by a constant infusion rate of insulin for 110 min. One of five different infusion rates of insulin was chosen for each patient to construct the dose-response curve for glucose disposal (M) at various plasma insulin levels by pooling the data from the different patients, as has been described previously[15,16]. In each group, three patients were studied at an insulin infusion rate of 1·2 milliunits kg^{-1} min^{-1}, three patients at 2·5 milliunits kg^{-1} min^{-1}, one patient at 5·0 milliunits kg^{-1} min^{-1}, one patient at 7·5 milliunits kg^{-1} min^{-1}, and one patient at 10·0 milliunits kg^{-1} min^{-1} The infusion of 20 per cent glucose solution was started 4 min after the start of insulin infusion. The infusion rate of the solution was adjusted to maintain plasma glucose at the baseline value for 2 h using a negative feedback algorithm[10] with slight modification. A blood sample for plasma insulin determination was taken every 10 min into a chilled tube, immediately separated and kept frozen until analysis The measurement of insulin was performed by radioimmunoassay using the double antibody technique.

By the method described above, blood glucose level during the study was maintained within 10 per cent of the baseline value and plasma insulin concentrations were also in steady state from 40 to 120 min after the beginning of insulin infusion (*Figure 1*) Glucose disposal from the plasma (M, mg kg^{-1} min^{-1}) was calculated from the mean rate of glucose infusion for 100 min (from 20 to 120 min after the analysis began) and space correction was made when the blood glucose value was unstable[10]. The metabolic clearance rate of insulin (MCRi, ml min^{-1} m^{-2}) was calculated as the insulin infusion rate divided by the increase in plasma insulin concentration above the baseline level (ΔI in *Figure 1*)[10]

Measurement of endocrine response

In five patients in each group, 24 h urine samples were collected to measure catecholamines starting on the day before operation until postoperative day 1 Peripheral venous blood samples were withdrawn for measurement of plasma cortisol before pre-anaesthetic medication, at about 1 h after skin incision, at about 30 min after completion of the procedure and at 08 00 h on postoperative day 1

Urinary catecholamines were determined using high-speed ion-exchange column chromatography and the automated trihydroxyindol method[17]. Plasma cortisol was measured by radioimmunoassay using the 'Gamma Cort' cortisol kit (Clinical Assay Co.).

Statistical analysis

All data were expressed as mean ± s.e.m Statistical analysis was performed using the paired and unpaired Student's *t* tests or Wilcoxon's rank sum test Multiple regression analysis was performed to produce dose-response curves and covariant analysis[18] was used to analyse the differences in the intercepts and the slopes of regression lines. *P* values $<0{\cdot}05$ were considered statistically significant.

Results

Euglycaemic insulin clamp test

The results of the euglycaemic insulin clamp test in group G are summarized in *Table 2*. The basal glucose increased significantly on postoperative day 1 ($P<0{\cdot}05$). The basal plasma insulin concentrations tended to increase postoperatively although the increase is not statistically significant. The steady-state plasma insulin concentrations increased proportionally to the insulin infusion rate. There was no significant difference between pre- and postoperative steady-state insulin levels. Values of MCRi increased postoperatively in four patients, decreased in four patients and did not change in one patient. There was no significant difference in MCRi between pre- and postoperative values. In every patient, postoperative M value was lower than the preoperative value. The difference between pre- and postoperative M values was significant ($P<0{\cdot}001$).

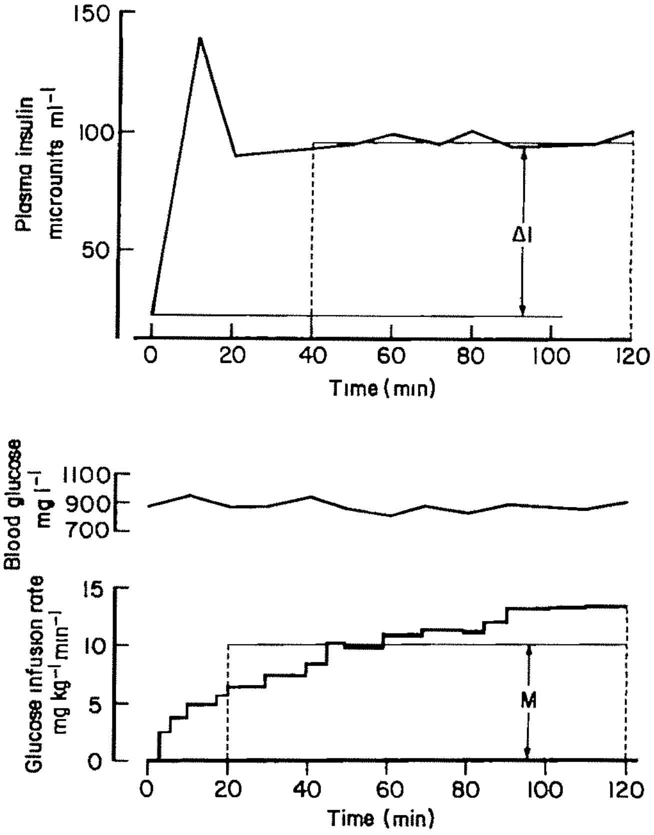

Figure 1 *Plasma insulin concentrations, blood glucose levels and glucose infusion rate during pre-operative euglycaemic insulin clamp test in a 62-year-old male patient. Glucose disposal (M) was defined from the mean rate of glucose infusion from 20 to 120 min of the study. ΔI, steady-state plasma insulin concentration (40–120 min)—basal plasma insulin concentration*

Table 2 *Results from euglycaemic insulin clamp in group G*

Patient no.	Insulin infusion rate (milliunits kg^{-1} min^{-1})	Basal glucose (mg dl^{-1})		Basal insulin (microunits ml^{-1})		Steady-state plasma insulin (microunits ml^{-1})		MCRi (ml min^{-1} m^{-2})		M (mg kg^{-1} min^{-1})	
		pre	post	pre	post	pre	post	pre	post	pre	post
1	1·2	84	118	5	10	35	42	1522	1422	8·0	2·9
2	1·2	90	98	7	14	55	86	1004	672	8·9	1·8
3	1·2	95	118	10	19	58	78	865	707	7·5	3·1
4	2·5	84	88	23	41	201	170	556	767	8·8	5·5
5	2·5	87	110	33	14	206	127	502	770	10·4	3·5
6	2·5	94	100	13	11	106	152	957	631	11·4	5·9
7	5·0	82	104	5	9	298	274	560	617	9·1	4·5
8	7·5	74	104	3	3	520	499	487	507	11·6	6·9
9	10·0	98	100	5	7	880	840	429	429	11·7	6·3
Mean		88	104	12	14	262	252	765	725	9·7	4·5
s.e.m.		3	3	3	4	92	87	119	95	0·5	0·6
		$P<0·05$		n.s.		n.s.		n.s.		$P<0·001$	

Group G, general anaesthesia group; pre, a pre-operative day; post, postoperative day 1; MCRi, metabolic clearance rate of insulin, M, glucose disposal from the plasma

Table 3 *Results from euglycaemic insulin clamp in group E*

Patient no.	Insulin infusion rate (milliunits kg^{-1} min^{-1})	Basal glucose (mg dl^{-1})		Basal insulin (microunits ml^{-1})		Steady-state plasma insulin (microunits ml^{-1})		MCRi (ml min^{-1} m^{-2})		M (mg kg^{-1} min^{-1})	
		pre	post	pre	post	pre	post	pre	post	pre	post
1	1·2	94	114	3	3	51	39	850	1134	8·5	3·9
2	1·2	96	106	10	7	43	32	1370	1829	5·9	5·1
3	1·2	88	100	8	7	54	42	978	1309	6·5	3·5
4	2·5	88	104	3	3	95	68	914	1290	10·6	5·8
5	2·5	98	94	3	3	92	69	929	1248	8·6	6·4
6	2·5	90	122	5	6	82	122	1057	726	6·7	5·2
7	5·0	86	92	5	5	172	199	1042	909	11·1	7·1
8	7·5	85	87	27	10	647	322	436	865	10·1	7·9
9	10·0	102	118	7	4	737	521	480	678	10·2	7·9
Mean		92	104	8	5*	219	157	895	1110	8·7	5·9
s.e.m.		2	4	3	1	91	55	96	120	0·6	0·5
		$P<0·05$		n.s.		n.s.		n.s.		$P<0·01$	

Group E, epidural analgesia group, pre, a pre-operative day; post, postoperative day 1
* $P<0·05$ compared with the postoperative value in group G. MCRi, metabolic clearance rate of insulin; M, glucose disposal from the plasma

The results of the euglycaemic insulin clamp test in group E are shown in *Table 3*. The basal glucose significantly increased postoperatively ($P<0·05$). The basal insulin did not change significantly postoperatively, but the postoperative value in group E was significantly smaller than in group G ($P<0·05$). There was no significant difference in steady-state plasma insulin level between pre- and postoperative values. MCRi increased in seven patients and decreased in two patients postoperatively, showing no significant difference between the pre- and postoperative values. Values of M decreased postoperatively in all patients in group E as well as in group G. Mean value of postoperative M was slightly greater in group E than in group G.

The dose-response relationship between the steady-state plasma insulin concentrations (I) and M in group G is shown in *Figure 2a*, and its conversion to M: log I relationship is shown in *Figure 2b*. There were statistically significant correlations between log I and M both in pre- and postoperative results. The intercept of the postoperative regression line was significantly smaller ($P<0·01$) than that of the pre-operative one, but there was no significant difference in slopes between the two lines, indicating a downward shift of the dose-response curve in *Figure 2a*. The dose-response curves of M against I and their conversion to regression lines in group E are shown in *Figure 3a* and *Figure 3b*. Statistically significant correlations were observed between log I and M both in pre- and postoperative results (*Figure 3b*). There was no significant difference in slopes between pre- and postoperative regression lines, but the intercept of the postoperative regression line was significantly smaller ($P<0·01$) than that of the pre-operative line. Comparing the pre-operative regression lines between group G and group E, there were no significant differences either in slopes or intercepts. Comparing the postoperative regression lines between the two groups, there was no significant difference in slopes, but the intercept in group G was significantly smaller ($P<0·01$) than in group E.

Endocrine response

Urinary adrenaline excretion in group G markedly increased on the day of operation and began decreasing slightly on postoperative day 1. The increase in urinary adrenaline on the day of operation was significantly smaller in group E than in group G ($P<0·05$). On postoperative day 1, adrenaline excretion in group E was less than in group G although the difference was not significant (*Table 4*).

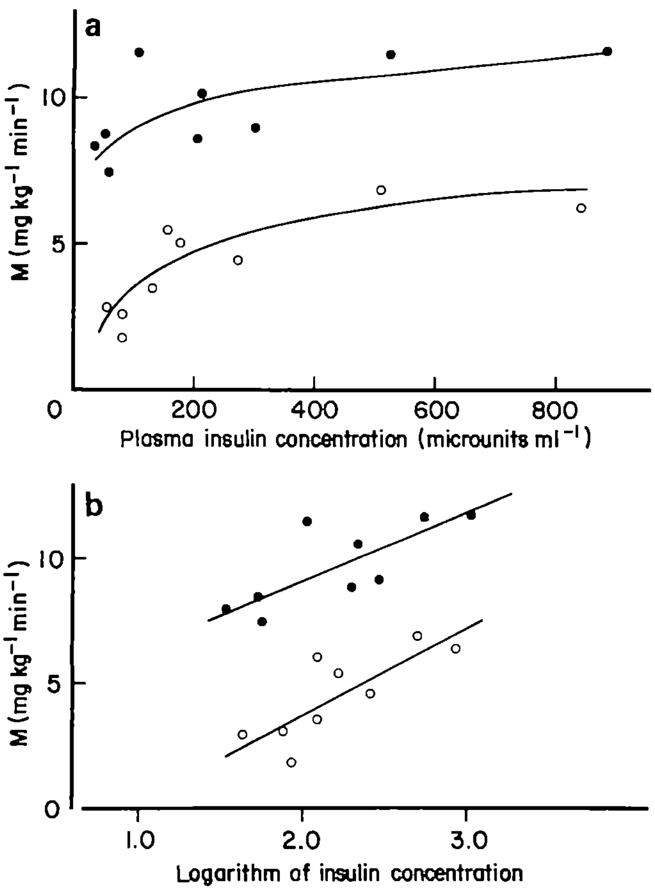

Figure 2 a *Dose-response curves of glucose disposal (M) at various plasma insulin concentrations (I) in group G,* b *correlation between M and log I in group G.* Figure 2b *shows the regression lines where the* x *value is converted to log I from I in* Figure 2a: ●, $4{\cdot}2+2{\cdot}5x$, $r=0{\cdot}74$, $P<0{\cdot}05$; ○, $y=-3{\cdot}3+3{\cdot}5x$, $r=0{\cdot}82$, $P<0{\cdot}01$. ●, *Pre-operative day,* ○, *postoperative day 1*

Urinary noradrenaline excretion in group G increased on the day of operation and further increased on postoperative day 1. In group E noradrenaline excretion did not increase significantly throughout the study period. The difference in urinary noradrenaline excretion between the two groups was significant on postoperative day 1 ($P<0{\cdot}05$) (*Table 5*).

Plasma cortisol concentrations in group G significantly increased during and shortly after surgery and on postoperative day 1. The pre-anaesthetic value of plasma cortisol was significantly higher in group E than in group G ($P<0{\cdot}01$). However, cortisol levels during and immediately after surgery were consistently lower in group E than in group G although the differences were not significant. On postoperative day 1, cortisol concentration was significantly lower in group E than group G ($P<0{\cdot}05$) (*Table 6*).

Discussion

The dose-response curves of M against I were used to define the mechanism of the disturbance of insulin action as previously described[11-13,15,16]. It has generally been accepted that the rightward shift of the dose-response curve (i.e. maximum response reached by a large dose of exogenous insulin) indicates a decrease in the number of active insulin receptors on cell membrane. In contrast, the downward shift of the curve (i.e. lowered maximum response by a considerably large dose of insulin) indicates a postreceptor deficit of insulin action[11-13]. In the present study the dose-response curves shifted downward postoperatively both in group G and group E patients as was clearly demonstrated by the decreased intercepts of the regression lines. This result is in accordance with those of Black *et al.*[15] and Brooks *et al.*[16] who have reported a postreceptor deficit in injured patients. Magnússon and Tranberg[19] recently studied the hypoglycaemic action of insulin using an infusion test in surgical patients and concluded that impaired glucose tolerance after elective surgery depends on a decreased action of insulin. Our present results offer further support for the contention that postoperative insulin resistance is due to a postreceptor binding effect.

When calculating the glucose disposal from the results of the euglycaemic insulin clamp test, slight underestimation is inevitable because of incomplete suppression of endogenous glucose production. It has been reported in healthy subjects that endogenous glucose production is completely suppressed at a blood insulin concentration of 100 microunits ml^{-1} (Refs 10, 11). However, Black *et al.*[15] have reported that a multiple

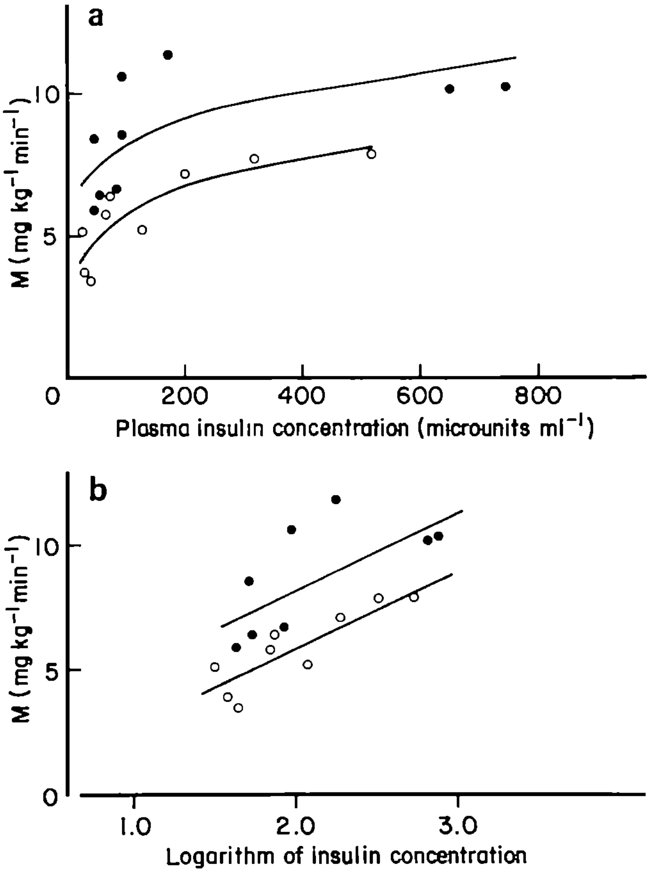

Figure 3 a *Dose-response curves of glucose disposal (M) at various plasma insulin concentrations (I) in group E;* b *correlation between M and log I in group E.* Figure 3b *shows the regression lines where the* x *value is converted to log I from I in* Figure 3a. ●, $y=2{\cdot}69+2{\cdot}86x$, $r=0{\cdot}68$, $P<0{\cdot}05$; ○, $y=-0{\cdot}63+3{\cdot}24x$, $r=0{\cdot}87$, $P<0{\cdot}01$. ●, *Pre-operative day;* ○, *postoperative day 1*

Table 4 *Urinary adrenaline excretion* ($\mu g\ day^{-1}$)

Group	Pre-operative day	Day of operation	Post-operative day 1
Group G			
Mean	6·6	28·6*	21·4†
s.e.m.	1·8	4·4	6·4
Group E			
Mean	5·2	12·3	19·8†
s.e.m.	1·3	3·0	5·5
P (*versus* G)	n.s.	<0·05	n.s.

Group G, general anaesthesia group ($n=5$); group E, epidural analgesia group ($n=5$); *$P<0{\cdot}01$ compared with pre-operative value, †$P<0{\cdot}05$ compared with pre-operative value

Table 5 *Urinary noradrenaline excretion* ($\mu g\ day^{-1}$)

Group	Pre-operative day	Day of operation	Post-operative day 1
Group G			
Mean	81·1	117·3	267·0*
s.e.m.	35·0	41·0	65·4
Group E			
Mean	40·3	52·3	65·2
s.e.m.	10·4	14·0	13·7
P (*versus* G)	n.s	n.s.	<0·05

Group G, general anaesthesia group ($n=5$); group E, epidural analgesia group ($n=5$); $^{*}P<0\cdot05$ compared with pre-operative value

Table 6 *Plasma cortisol concentrations* ($nmol\ l^{-1}$)

Group	Before pre-medication	1 h after skin incision	30 min after surgery	Post-operative day 1
Group G				
Mean	247	630*	825*	560*
s.e.m.	8·8	71·1	119·4	37·1
Group E				
Mean	311	529*	734*	306
s.e.m.	13·4	44·2	83·1	60·8
P (*versus* G)	<0·01	n.s.	n.s.	<0·05

Group G, general anaesthesia group ($n=5$); group E, epidural analgesia group ($n=5$); $^{*}P<0\cdot01$ compared with the value before premedication

trauma patient showed 91 per cent suppression of endogenous glucose production at the insulin concentration of about 300 microunits ml^{-1}. Regarding our elective surgery as moderate injury, endogenous glucose production is assumed to be more suppressed that in severely injured patients. Even when unblocked glucose production of 10 per cent was added to each of the postoperative M values in our results, a downward shift of the curves was still observed.

We have demonstrated in the present study that the degree of postoperative disturbance of insulin action evaluated by the insulin clamp technique was less in group E patients than in group G patients. Magnússon *et al.*[20] studied patients undergoing inguinal herniorrhaphy using a bolus insulin infusion test and reported that hypoglycaemic action of insulin during surgery was reduced under general anaesthesia but was unchanged under epidural anaesthesia. Our results indicate a mitigated postreceptor deficit of insulin action by epidural analgesia in patients undergoing surgery of greater magnitude.

The acquired plateau of blood insulin concentration during insulin infusion was lower in the present study compared with the reported values[11,15,21]. The reason for this difference between our results and those reported by others is unclear. In injured patients MCRi values have been reported to be greater than normal[15,21], and this increased MCRi was explained by the increased blood flow to the organs which contribute to insulin clearance[22]. On the other hand, Magnússon *et al.*[20] reported that insulin clearance decreased during herniorrhaphy under general anaesthesia but was unchanged under epidural anaesthesia. In the present study, however, MCRi did not show any consistent changes after surgery and epidural analgesia did not modify the MCRi change. The mechanism of the change in MCRi after surgery is unknown.

Eigler *et al.*[6] reported that simultaneous infusion of glucagon and adrenaline induced decreased peripheral glucose utilization in healthy dogs. Bessey *et al.*[7] reported that insulin resistance developed in healthy volunteers who received a combined infusion of cortisol, glucagon and adrenaline. Thus, those catabolic hormones are thought to have an important role in impaired glucose utilization. On the other hand we have previously reported that postoperative analgesia with epidural morphine resulted in a reduced response of cortisol, catecholamines, and glucagon following elective gastrectomy[23]. Endocrine responses were also suppressed in group E patients in the present study compared with group G patients. This may confirm that suppression of the endocrine response to surgery by epidural analgesia is responsible for the altered insulin resistance, which was postulated from the change in insulin/glucose ratio in our previous report[2].

In addition to the endocrine mediators, interleukin-1 or related molecules are considered to be possible mediators of catabolic reaction to critical illness. However, their role in stress reaction to clean elective surgery is not clear. Watters *et al*[24] reported that injection of etiocholanolone (inducer of interleukin-1) into normal volunteers did not suppress glucose disposal which was evaluated by the insulin clamp technique. There is no supportive evidence that interleukin-1 is a cause of disturbed insulin action. It has been suggested that accelerated oxidation of free fatty acids may inhibit glucose transport after surgery[19,25]. Hypophosphataemia has been shown to cause tissue insensitivity to insulin[19,26] However, whether change in the turnover rate of free fatty acids or change in serum phosphate level induces insulin resistance after surgery is at present unknown.

In conclusion, euglycaemic insulin clamp studies revealed that insulin resistance following elective abdominal surgery is due to a postreceptor deficit of insulin action, which is improved by inhibiting nociceptive neural stimuli with epidural administration of local anaesthetic and morphine. The improvement of the postoperative insulin resistance was associated with a reduced catabolic hormone response.

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Case report

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Permanent transrectal drainage of a diverticular-related abscess with a double-ended pigtail catheter

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Percutaneous drainage of diverticular abscesses can reduce morbidity and may facilitate a subsequent single-stage colonic resection$^{1-3}$. We report the percutaneous transrectal drainage of a subcutaneous diverticular-related abscess occurring 10 years after defunctioning the colon for complicated diverticulitis.

Case report

A 73-year-old woman weighing 115 kg presented in 1975 with left-sided abdominal pain and increasing constipation. A sigmoidoscopy was normal, but a barium enema demonstrated diverticular disease with considerable sigmoid spasm. She was treated with a high fibre diet, but her symptoms continued unabated and 8 months later she required a further hospital admission when a tender mass was palpable anterior to the rectum. This did not resolve with conservative treatment and, at laparotomy, was found to be inflammatory and could not be safely removed. An end colostomy was formed, the distal end of the colon being brought out at the lower end of the wound. A distal loop barium enema 2 months later showed continuing sigmoid obstruction, but her symptoms had resolved. She subsequently managed well until 10 years later when another episode of abdominal pain and distension necessitated further investigation. A barium colostomy enema showed diverticular disease in the segment of colon proximal to the stoma, but the distal colonic segment was not investigated, the mucous fistula had completely retracted and was no longer visible

Three months after the barium enema, an abscess appeared in the anterior abdominal wall adjacent to the colostomy. This was drained, but a sinus persisted at the drainage site with continuing haemopurulent discharge which was impossible to control or adequately dress because of her obesity and a large incisional hernia. A sinogram demonstrated an abscess cavity which was laid open under general anaesthetic with placement of a drain, this fell out within a week. Discharge from the sinus subsequently persisted, and a further sinogram 3 months later showed a fistula connecting the abscess with the distal colonic loop. To assist drainage, an angiographic pigtail catheter was placed into the abscess cavity in the fistula track through the abdominal wall opening. The catheter fell out shortly afterwards, so the fistula was re-explored with angiographic catheters and guide-wires, and a wire was placed through the abscess, along the fistula track into the distal colonic loop, and out through the anus. With a long wire thus placed transcorporeally, a Ring drainage catheter was introduced through the anus, and its tip placed in the abscess cavity, facilitating drainage into the bowel.

This catheter fell out after 2 weeks, and was replaced using a similar technique, but this time a 6·5 F double-ended pigtail catheter, made to the appropriate length, was placed along the transcorporeal guide-wire so that one end lay in the abscess subcutaneously and the other end in the distal colonic loop. Mucopus drained per rectum for 1 month, and the abdominal opening of the fistula then dried up and has not recurred 1 year later

Discussion

The chronic inflammatory sequelae of complicated diverticulitis are often difficult to manage surgically^{4}. A non-surgical approach may therefore be valuable. This elderly obese, chronic bronchitic patient who had had three previous abdominal operations presented a considerable challenge to conventional surgical management of her complicated diverticular fistula and related abscess. Adequate internal drainage of her abdominal abscess through the rectum using an in-dwelling catheter has given excellent symptomatic relief without recourse to surgery.

Although percutaneous drainage of diverticular abscesses under CT control has been used to reduce morbidity before definitive surgery$^{1-3}$, permanent non-surgical transrectal drainage of such abscesses has, to our knowledge, not been reported and may offer considerable advantages in management in selected patients.

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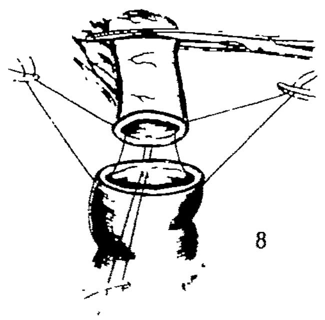
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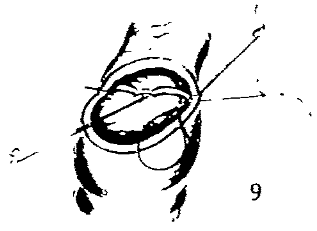
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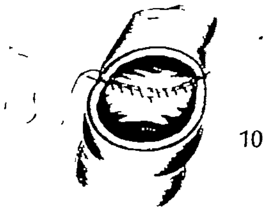
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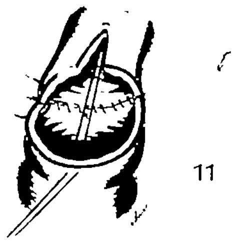
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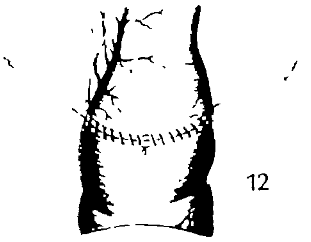
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Tuberculous cervical abscess: comparing the results of total excision against simple incision and drainage

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In 40 patients with tuberculous cervical abscesses a prospective study was undertaken to determine the results of surgical treatment by either total excision or incision and drainage, together with 6 months of chemotherapy in both groups. While both procedures were well tolerated, the results showed that 17/22 (77 per cent) of those having a simple drainage procedure required a second operation to excise the residual infected lymph glands because of persistent sinus discharge, recurrent abscesses or enlarging lymphadenopathy. In contrast, 17/18 (94 per cent) of those having total excision as the primary procedure had no local ward problem afterwards. Most of the patients remained asymptomatic after completion of the chemotherapy but small painless lymph nodes might still be palpable during follow-up at 2 years.

Keywords: Tuberculous cervical abscess, incision and drainage, total excision, chemotherapy

The treatment of cervical tuberculous lymphadenopathy is controversial[1–6] with drainage being advocated by some and total excision by others. A prospective study comparing total excision against simple incision and drainage, both with chemotherapy, was undertaken.

Patients and methods

Between 1978 and 1984, 199 patients presented to the Department of Surgery, University of Hong Kong, with tuberculous lymphadenopathy. The majority, 181 patients, had the cervical glands affected while the remaining 18 patients had lymphadenopathy elsewhere. Among the 181 patients, 40 (22·1 per cent) had an abscess or a discharging sinus at presentation. These 40 patients were assigned alternately to either total excision or incision and drainage of the abscess, but true randomization was not maintained because two patients refused to have general anaesthesia for total excision as the initial procedure. This has resulted in a slightly greater number of patients undergoing incision and drainage.

Total excision was done under general anaesthesia, and the abscess wall with the adjacent and deep-seated lymph nodes were excised. The wounds were closed primarily. Most incision and drainage procedures were done under local anaesthesia and the wounds were left open for dressing. The pathological specimens were examined for acid-fast bacilli with Ziehl-Neelsen stain and cultured in Löwenstein-Jensen medium; histological examination was also carried out. Either bacteriological or pathological evidence was acceptable for the diagnosis of tuberculosis[7,8]. Antituberculosis chemotherapy was started for all patients and continued for 6 months. The standard regimen used in treating pulmonary tuberculosis was employed and consisted of streptomycin 1 g, INAH 15 mg/kg, rifampicin 450 mg/600 mg and pyrazinamide 2·5 g three times per week[9].

All patients were followed up regularly The condition of the wound and the presence of residual lymph nodes were noted. A persistent sinus was considered to be present if the wound had significant inflammation and discharge after 3 weeks and a track connecting to a deeper tissue plane could be demonstrated on examination. Re-excision was considered for those who had a persistent sinus for more than 3 weeks or for those who developed a new abscess.

Results

The clinical characteristics of the patients are shown in *Table 1*. All the 40 patients in the study were proven to have tuberculous infection by either typical histological features or bacteriological confirmation. All the mycobacteria cultured were typical *Mycobacterium tuberculosis* and sensitive to the standard drugs.

There were 22 patients in the incision and drainage group and these were followed up for at least 2 years except one patient who defaulted after 6 months. Nerve injury or postoperative bleeding did not occur. The wounds had healed in only five patients 3 weeks after the operation; four of them remained asymptomatic at 2 years but one patient had a recurrent abscess one month later which required further surgery. Persistent wound discharge and sinus formation occurred in 16 patients; 11 of these 16 patients had re-excision of the residual sinus tract and lymph nodes and remained well. Five patients decided to persist with conservative treatment and, although initial skin healing was achieved temporarily, four wounds subsequently broke down and resulted in a persistent sinus requiring further operative intervention. One patient had a rapidly enlarging lymph node and required further re-excision shortly after the initial drainage procedure. The wounds healed in all the patients who underwent re-excision after a further mean time of 3·2 weeks. At the end of 2 years, 17 patients were totally asymptomatic and 4 patients had small residual lymph nodes <1 cm in diameter but the wounds remained healed (*Table 2*).

Table 1 *Clinical, bacteriological and pathological characteristics of patients*

	Incision group $n=22$	Excision group $n=18$
Mean age	31 (15–62)	29 (18–76)
Sex ratio (M:F)	1:2	1.3·5
Right side abscess	10	12
Left side abscess	11	5
Bilateral abscess	1	1
AFB smear +ve	14 (64%)	11 (61%)
AFB culture +ve	10 (45%)	5 (28%)
Histological features of tuberculosis	20 (91%)	17 (94%)

AFB, acid-fast bacilli

Table 2 *Follow-up results*

	Incision group $n=22$	Excision group $n=18$
Incomplete follow-up	1	1
Operative complications	0	0
Persistent wound problem after 3 weeks	16 (73%)	1 (6%)
Re-excision needed	17 (77%)	1 (6%)
Asymptomatic at 2 years	17 (77%)	14 (78%)
Residual lymph nodes at 2 years	4 (18%)	3 (17%)

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In the excision group there was no nerve injury, bleeding or anaesthetic complication which occurred from the surgical excision done under general anaesthesia. The wounds healed in 17 patients after a mean of 2·5 weeks. On follow-up, one patient had died of a stroke 2 months later and two patients had a recurrent sinus formation which healed within 2 weeks on conservative treatment. The other 14 patients remained well for 2 years. Persistent wound discharge 3 weeks postoperatively occurred in only one patient; at re-exploration, residual infected lymph nodes located around the sternomastoid muscle were found and these were probably missed during the initial excision. At the end of 2 years, 14 patients were completely asymptomatic and 3 patients had small residual lymph nodes (*Table 2*).

Discussion

Tuberculous lymphadenopathy is the most common form of extrapulmonary tuberculosis[8,10]. Jones and Campbell[11] have described the natural history of tuberculous lymphadenopathy. When abscess formation occurs, its formidable appearance often stops surgeons from proceeding to a total excision. A simple drainage procedure is preferred with the residual disease left to be treated by chemotherapy[5,10,12], but such treatment has been found to be inadequate and further surgery may be necessary to excise the residual infected tissue[13]. To save the patient a second operation and a prolonged convalescent period, primary total excision may be the method of choice.

Our results showed that local wound problems occurred much more frequently after a drainage procedure. More than 70 per cent of these patients had persistent wound problems 3 weeks after surgery in contrast to those who had total excision where primary wound healing was obtained in more than 90 per cent of the patients. Such persistent wound problems usually indicate residual infected lymph nodes and are unlikely to heal with continued conservative treatment. However, all wounds healed 3 weeks after a total excision of the lymph nodes, whether this was a primary or secondary procedure, and remained so 2 years later.

Simultaneous chemotherapy is probably useful in eradicating any residual organism left behind after surgical excision. The exact drug combination and duration of the antituberculous medication still need to be defined by other studies. We have adopted the standard drug regimen used for treatment of pulmonary tuberculosis. This was well tolerated by all the patients and when combined with adequate excision of the infected tissue gave a good control of the cervical tuberculous abscesses on a 2-year follow-up although small static lymph nodes might persist for a long time after the completion of treatment. We have found that they remained small, painless, and static in size with no sign of inflammation.

This study demonstrated that total excision of the tuberculous abscess cavity and the infected lymph glands can be done safely as a primary procedure. With chemotherapy, local control of the disease was achieved in more than 90 per cent of the patients. We would thus advocate total excision as the primary procedure for patients with cervical tuberculous abscesses and early re-excision for persistent discharging wounds.

Acknowledgement

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Surgical management of substernal goitre

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This paper presents the clinical features and problems in the management of 34 patients with substernal goitre. Complete evaluation of the mediastinum relied on computed tomography. Thyroid function tests were performed routinely and showed a clinically underestimated incidence of hyperthyroidism (44 per cent). The incidence of occult malignancy in substernal goitres was high (12 per cent). In the majority of patients (88 per cent) the substernal goitres were removed by a collar incision. Four cases of goitres located in a retrotracheal position required a combined cervical and sternotomy approach. None of the 34 patients died. Transient postoperative hypocalcaemia was found in 41 per cent of our patients. The presence of a substernal goitre is an indication for resection based on the risk of malignancy, the risk of acute respiratory distress, the high incidence of thyrotoxicity and a low surgical morbidity.

Keywords: Substernal goitre, mediastinal tracheostomy, sternotomy, thyrotoxicity

Substernal goitres were described as early as 1749 by Haller[1], but the first confirmed report of this pathology was by Klein[2] in 1820. The surgical implications of this type of thyroid swelling are described by Lahey and Swinton[3], Crile[4], Higgins[5], Joll[6], Wakeley and Mulvany[7] and more recently by Katlic *et al.*[8,9], all of whom collected data from tertiary referral centres where large numbers of thyroid swelling were managed.

Substernal goitres have not been uniformly defined in relation to the proportion of the gland within the thorax, its relationship to the mediastinum and the origin of its blood supply. They have been referred to as retrosternal, subclavicular, intrathoracic, mediastinal, aberrant or wandering, spring or goitre 'plongeant'. We and others[9–11] have chosen to refer to any goitre in which greater than 50 per cent of its mass is inferior to the thoracic inlet as substernal or intrathoracic (*Figure 1*).

Patients and methods

Of the 170 patients undergoing thyroid surgery between January 1982 and December 1986, 34 (20 per cent) had substernal goitres.

Operative technique

A standard operative approach was used for all patients undergoing thyroid surgery. In the case of retrosternal goitres, emphasis was placed on the essential steps of ligating the superior thyroid artery and freeing the upper pole of the thyroid before beginning delivery of the gland from its retrosternal position. The inferior pole relations (i.e. recurrent laryngeal nerve) can be difficult to identify until the retrosternal component has been mobilized. The recurrent laryngeal nerve is at risk once more as it drifts anteriorly and lies within the ligament of Berry, and this is true of any thyroidectomy. The mobilization was done in a subcapsular fashion, using a blunt dissection technique deep to the pretracheal fascia but outside the true thyroid capsule. This avoided injury to the pleural apices, inferior thyroid veins, recurrent laryngeal

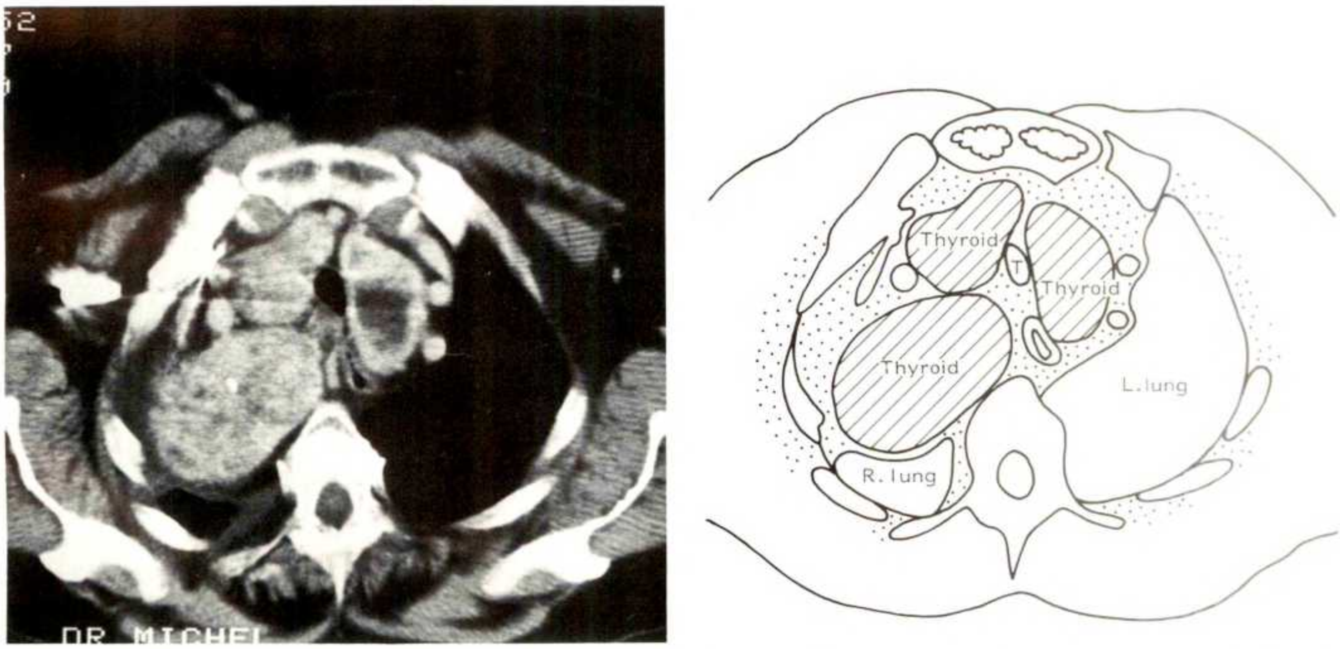

Figure 1 *Computed tomographic scan of substernal goitre showing a bilobar extension behind the sternum and a large intrathoracic component on the right side. T, trachea*

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nerve and the thoracic duct. In no case was the true capsule breached for piecemeal delivery of the gland. Extraction of goitres located in a retrotracheal position proved more difficult to perform. In these cases, a combined cervical and sternotomy approach was used. Bilateral substernal goitres were subjected either to a lobectomy plus subtotal contralateral lobe resection or to a bilateral subtotal resection. Postoperative drainage was achieved by closed suction drain brought out lateral to the incision and removed after 48 h. When sternotomy was performed, suction drains were also placed in the mediastinum and removed after 48 h.

Table 1 *Symptoms and signs in 34 patients with substernal goitre*

Symptoms and signs	*n*	%
Cervical mass	25	73
Hyperthyroidism	15	44
Hoarseness	9	26
Dysphagia	9	26
Dyspnoea	7	20
Cough	4	12
Stridor	3	9
Unilateral vocal cord paralysis	1	3
Transient ischaemic attacks	1	3
None	4	12

Table 2 *Accuracy and sensitivity of pre-operative studies*

Study	No. of patients examined	No. of studies suggesting substernal extension	Sensitivity (% correct)
Chest X-ray	34	20	59
Thyroid scanning	30	23	77
Barium swallow	14	10	71
Mediastinal tomogram	10	9	90
Computed tomographic scanning	10	10	100
Arteriography	2	2	100
Ultrasound	2	2	100

Results

The 34 patients comprised 22 women and 12 men whose mean age was 61 years (range 33 to 80; median 65 years). Fifteen had received thyroid suppressive medication before referral without benefit. Four had been treated with iodine-131 and one had undergone a previous thyroid resection 5 years previously. The majority of patients were classified as class 2 or 3 according to the American Society of Anesthesiologists (ASA) Physical Status Classification. The commonest presenting symptoms were neck swelling and thyrotoxicosis (*Table 1*). Four patients presented with unrelated complaints and were noted incidentally to have thyroid swellings. Thyroid function tests were carried out on all 34 patients. Fifteen (44 per cent) were found to be thyrotoxic on the basis of the tests. The pre-operative studies carried out to determine the presence of retrosternal involvement are indicated in *Table 2*. All had postero-anterior and lateral chest radiographs. Of the 34 patients, 20 were shown to have soft tissue swellings, 15 had tracheal deviation and 11 had soft tissue calcification in the area of the mass. Standard chest tomography and computed tomography clearly demonstrated the retrosternal extension in 19 patients. The degree of such downward extension varied but in ten patients reached the aortic arch (*Figure 2*) or carina.

In 30 patients, a cervical approach alone was adequate for resection of these lesions (*Table 3*). The remaining four patients required the addition of a median sternotomy because of retrotracheal extension of the goitre in three. The fourth patient had an invasive papillary carcinoma involving the larynx and trachea extensively (*Figure 3*). In this case a total cervical

Table 3 *Type of incisions and of operative procedures*

Incision	Left lobectomy	Right lobectomy	Bilateral subtotal thyroidectomy
Collar	5	6	19
Collar and sternotomy	0	1	3*

* One case required elective transmural tracheostomy

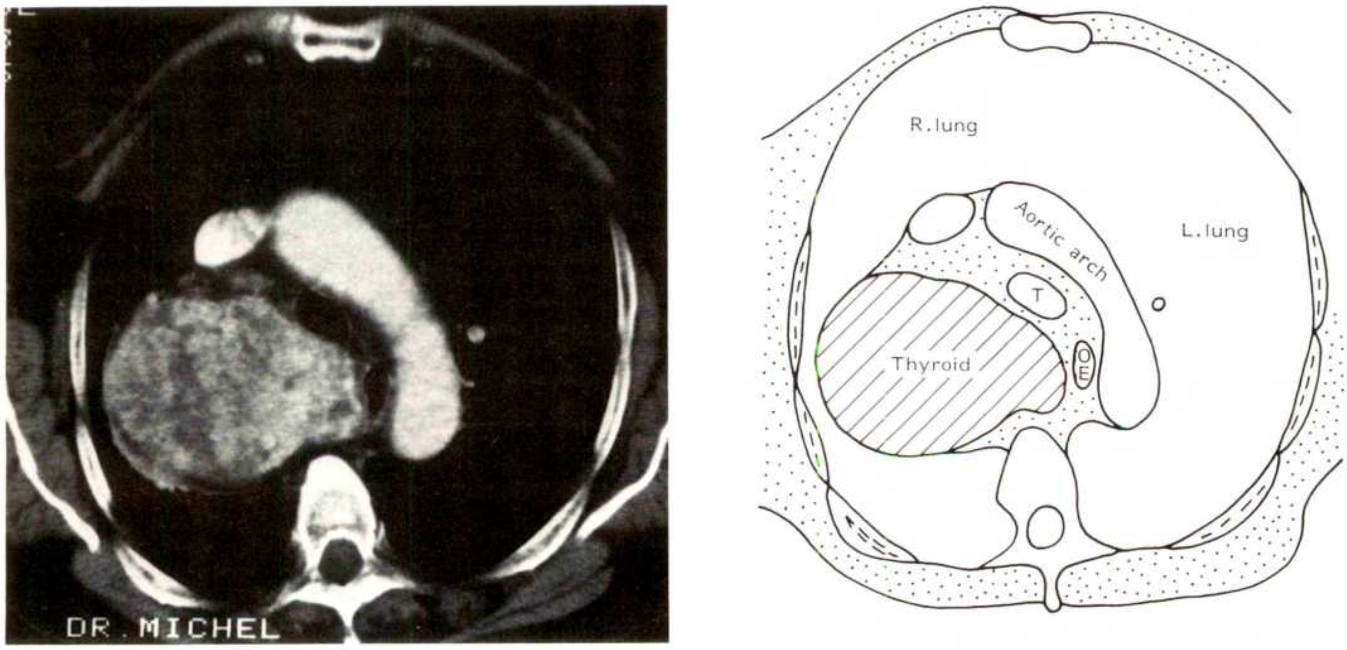

Figure 2 *Computed tomographic scan of substernal goitre extending downward to the arch of the aorta and displacing the trachea and oesophagus to the left. T, trachea; OE, oesophagus*

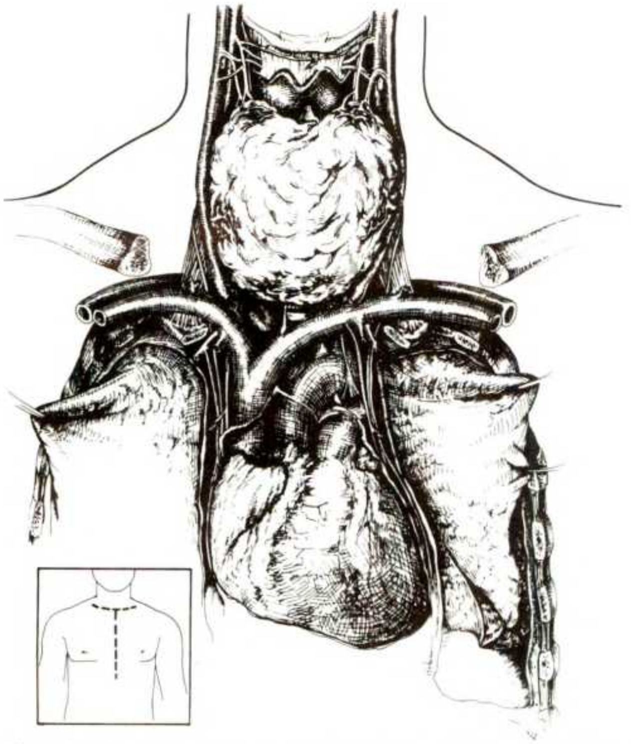

Figure 3 *Illustration of the extent of the lesions found at operation of the patient with papillary carcinoma involving the larynx and trachea. (Inset: type of incision)*

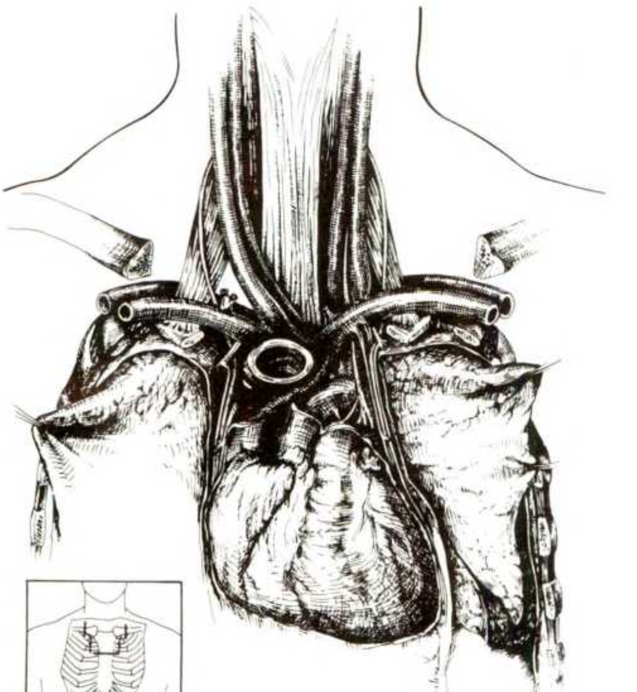

Figure 4 *Illustration of the modified mediastinal tracheostomy*[11] *performed after resection of the lesions (patient from* Figure 3) *and after transposition of the trachea below the innominate vessels. (Inset: osteotomies performed in order to complete the procedure)*

exenteration was performed. Peritracheal involvement necessitated the use of a mediastinal tracheostomy as described by Grillo[11] (*Figures 3* and *4*). In order to obtain sufficient length for creation of the tracheostomy, the 2·5 cm tracheal stump was transposed inferiorly and to the right of the innominate vessels—a manoeuvre which also prevented erosion of these vessels by the tracheal cartilages (*Figure 4*).

In another patient a Zenker's diverticulum was resected simultaneously with a bilateral substernal goitre through a collar incision.

It is of note that the patients requiring an intrathoracic approach to their lesions were all at significant risk of trauma to neurovascular and other related anatomical structures and a purely cervical approach would have increased this risk. Furthermore, where retrotracheal involvement is present, we believe that complete and safe removal of the lesion is only possible if a sternotomy is performed.

Pathology

The commonest histological diagnosis was non-toxic multinodular goitre accounting for 47 per cent of cases (16 patients). A further ten patients had toxic nodular goitres (29 per cent). Carcinomas were present in four instances (12 per cent) and the remaining four patients had solitary toxic adenomas. Two other patients were found to have focal thyroiditis. The mean weight of the lesions was 120 g (range 40–460 g), with a mean largest dimension of 9 cm (range 4–21 cm).

Complications

There were no perioperative deaths and no major complications. Twenty patients (59 per cent) had minor complications (*Table 4*). The most frequent minor complication was transient hypocalcaemia, occurring in 14 patients (41 per cent). Only four cases required calcium supplements for more than a week and none required more than 3 weeks of treatment.

Discussion

Reeve *et al.*[12] found that the incidence of substernal goitre was 1 in 5040. On the basis of mass radiographic surveys of the general population, it was 1 in 2030 among women over 45 years old. Wychulis *et al.*[13] reported a 5·3 per cent incidence of substernal goitres from a series of 1064 mediastinal tumours. This report, in common with others[3,4], describes the incidence of substernal goitre in relation to the total number of thyroidectomies performed. Reported incidences range from less than 1 per cent to more than 20 per cent. Over a 5-year period in the authors' personal series of 170 thyroidectomies, 34 goitres were found to be substernal.

Substernal goitres are commoner in patients aged over 50 years[4,8]. The mean age in this series was 61 years (33–80 years). There is a female preponderance (22:12) in this study in contrast to the ratios of 3–4:1 reported by others[10].

Substernal thyroid swellings are almost always downward extensions of a normally placed thyroid gland. Truly ectopic thyroid tissue may occasionally give rise to mediastinal goitres[14,15]. When present, these ectopic glands receive their blood supplies from the aorta, innominate or internal mammary arteries. In one case in this series, despite the continuity between the thoracic and cervical portions of the gland, collateral blood

Table 4 *Morbidity and mortality in 34 patients with substernal goitre*

	n
Deaths	0
Complications	
Transient hypocalcaemia	14*
Episode of rapid atrial fibrillation	2
Wound seroma	1
Temporary dysphagia (1 month)	1
Pleural effusion	1
Pulmonary embolism	1
Recurrent nerve injury	0

* Only four patients required oral supplementation of calcium for 1–3 weeks

vessels from the right internal mammary artery supplied the intrathoracic moiety.

The right and left lobes of the thyroid may equally give rise to substernal goitres[8,9,16]. Most are located in the anterolateral mediastinum, but few are limited to the pretracheal space. Between 10 and 15 per cent of substernal goitres are posterior, at least in part, and by definition will have a retrotracheal component[8,17–19]. Four such patients (12 per cent) are included in this report.

The clinical presentation in this cohort of patients is similar to that in other studies. One interesting presentation, first reported by Lesoin[20] and more recently by us[21], is that of 'thyroid steal syndrome' in which large thyroid vessels associated with abnormal carotid or vertebral arteries caused transient ischaemic attacks. The symptoms resolved after thyroidectomy. Superior vena caval obstruction is a rarity and when present a thyroid malignancy is often the cause. Others have reported this complication as a result of benign substernal goitre[22–26]. The incidence of thyrotoxicity in this series was greater than that quoted by others[8,10]. This finding confirms the need for thyroid function testing on all patients before thyroid surgery. Treating all thyrotoxic patients with β-blockers before thyroidectomy has not been found to be necessary in our experience, provided a euthyroid state can be obtained preoperatively. Pain and tenderness are uncommon and signify abscess formation, intrathyroid bleeding or malignancy[27,28].

Typically the thyroid swellings that give rise to substernal goitres may be solitary adenomas, but are more usually multinodular[9,28,29]. Carcinoma has been reported in 2–3 per cent of substernal goitres[8,9,12,18,29]. The 12 per cent incidence of occult malignancy reported in this series is remarkably high. Excision of all substernal goitres is advocated because malignant change may be insidious[8].

The diagnosis of substernal goitre is suggested by the presence of a mediastinal mass associated with a cervical goitre, previous thyroid surgery, high tracheal deviation, movement on swallowing and a positive thyroid scintigraphy. The differential diagnosis of anterior mediastinal mass may none the less be difficult and certain investigations can assist diagnostically. Plain chest radiography is the most cost-effective investigation[8], but this and other series[10] revealed normal chest radiographs in 19–41 per cent of cases. The sensitivity of this investigation as a screening test is low. The addition of linear tomography increases the sensitivity of the test to 90 per cent.

Complete evaluation of the mediastinum currently relies on computed tomography (*Figures 1 and 2*) but magnetic resonance imaging may become the diagnostic investigation of choice for the future.

There is controversy as to the value of a barium swallow. Deviation and/or compression of the oesophagus was found in more than 70 per cent of patients in current series and elsewhere[30]. However, the investigation may be surprisingly normal even when extensive carcinoma involving the trachea is present[8,31].

Venography may be indicated when superior vena caval obstruction is present, although the clinical findings in this condition usually provide the diagnosis without venography. Digital substraction arteriography is an important diagnostic modality in difficult cases where the vascularization has to be precisely outlined, such as in totally intrathoracic goitre.

The use of thyroid isotope scans is controversial in the preoperative investigation of these cases[9]. In this series the investigation was useful in 76 per cent of the patients who underwent technetium scan in that it showed either decreased or heterogeneous uptake in an enlarged gland. However, a negative scan cannot be diagnostic because the majority of these lesions have little or no functioning thyroid tissue. Iodine scan is better at imaging substernal gland.

Treatment

Treatment of large goitres with thyroxine, radiotherapy or iodine-131 is largely ineffective[32–34] and thyroidectomy is preferable for symptomatic disease.

Judd *et al.*[29] from the Mayo Clinic published in 1960 a review of the evolution of the surgical approach to substernal goitre. They expressed the view that increasing interest and familiarity with thoracic surgical techniques had led to an overemphasis of the thoracic approach.

Posterior mediastinal extensions of substernal goitres may be best approached using a sternotomy because traction on these lesions may prove hazardous; this is also the case when the lowermost pole of the goitre cannot be palpated. However, despite the fact that, in general, sternotomy is rarely necessary, we believe that this approach is safer for retrotracheal (as opposed to anterior) retrosternal goitres. In addition, indications for sternotomy[10] include recurrent intrathoracic goitre, emergency surgery for airway obstruction, superior vena caval obstruction, low lying carcinoma with cervical lymph node involvement, diagnostic uncertainty and retrotracheal goitre that extends to the level of the aortic arch on computed tomographic assessment.

Posteriorly situated substernal goitres can be difficult to deliver despite the addition of sternotomy to the standard cervical approach. It has been suggested by some[17,35] that posterolateral thoracotomy be undertaken in these cases when the cervical route is found to be inadequate. This has not been found to be necessary in this series or others on the subject.

Carefully selected patients with massive mediastinal involvement from thyroid cancer may benefit from cervical exenteration with mediastinal tracheostomy[11,36].

If surgical exploration reveals that one lobe is macroscopically normal or even atrophic, and after having obtained results of frozen section, we prefer to leave the normal lobe in place in order to avoid postoperative hypothyroidism especially in elderly patients.

The presence of a substernal goitre in all but the highest risk patients is an indication for resection based on the risk of malignancy, the risk of acute respiratory distress, the high incidence of thyrotoxicity and the lower surgical morbidity.

Extensive imaging is unnecessary providing computed tomography is available. Thyroid function tests, however, should be performed routinely because of the underestimated incidence of hyperthyroidism.

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Surgical drains

Means to provide drainage have changed radically from the periods in which metal, tubes, bone, glass, wicking, and combinations of gauze and rubber were used. The tapered lead and bronze tubes advocated by Celsus were followed by the bits of linen of Guy de Chauliac. Subsequently, the familiar Penrose wick and later the cigarette drain were described. These methods are all passive and depend on capillary action.

The surgical fraternity slowly became aware that passive drainage was inadequate. About 90 years ago, Mr George Heaton, a Fellow of the Royal College of Surgeons practising in Birmingham, UK, described a simple form of siphon action to 'remove even the smallest quantity of fluid as it collects in the cavity to be drained' (Heaton G. Note on the drainage of large cavities after surgical operations. *Br Med J* 1898; **24**: 207–8).

Such pioneering thinking is not unexpected when a review is made of his earlier years. He was the recipient of many scholarships and academic honours and apparently attended his surgical practice with zest. During his later years, he became consulting surgeon and an examiner in surgery at the University of Oxford, UK.

The concept of closed-suction drainage as it is practiced today had its inception in this simple and well illustrated publication by Mr Heaton. He has never received adequate acknowledgement for his contribution. Indeed, the list of his publications as noted in the *Lives of the Fellows of the Royal College of Surgeons of England* does not include this reference. The time is more than past for the recognition of Mr Heaton for his idea.

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Renal transplantation: the non-starters

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Renal transplants do not always function immediately and this non-function may be related to poor long-term graft survival. The causes of this primary non-function (PNF) are poorly understood. The incidence of PNF in 106 consecutive renal transplants was found to be 57 per cent. Using stepwise logistic regression analysis of 20 prospectively collected variables for each transplant two have been found to be positively associated with PNF of the transplant: (1) the use of cyclosporin as an immunosuppressant and (2) a second warm ischaemia (anastomosis) time of more than 30 min. It is proposed that the use of cyclosporin be restricted in the early post-transplant period until initial function of the transplant is established. The surgical procedure of kidney transplantation should be planned to minimize the anastomosis time prior to recirculation of the graft.

Keywords: Renal transplants, primary non-function, cyclosporin, warm ischaemia

In the 'pre-cyclosporin era', primary non-function (PNF) of transplanted kidneys did not appear to be associated with poor longer term graft function. It has recently been found that PNF in cyclosporin-treated recipients *is* associated with a poor long-term outcome[1]. A 72 per cent 1-year graft survival with PNF compared with 89 per cent in those grafts with immediate function[2] and 2-year graft survival of 58 per cent *versus* 72 per cent[3] have been reported. The identification of any aetiological factors associated with PNF might, therefore, lead to improved graft survival.

The aim of this study was to investigate prospectively the PNF rate in 106 consecutive renal transplant recipients in a single centre and to identify any factors which, singly or in combination, were associated with PNF.

Patients and methods

A consecutive series of 106 renal transplants over an 18-month period was studied. Prospective data collection was performed on the following variables: initial warm ischaemia, second warm ischaemia (anastomosis time), cold ischaemia (ice storage time), donor age, donor systolic and diastolic blood pressure, donor urine output in the 24 h up to retrieval, kidney perfusate (Collin's, Marshall's, Sach's, citrate), HLA A, B and DR mismatch between donor and recipient (scored 0 to 6), donor type (living/cadaveric), recipient systolic and diastolic blood pressure, recipient age and sex, recipient urine output per 24 h, presence of panel-reactive lymphocytotoxic antibodies in recipient, form of dialysis in recipient (haemodialysis, chronic ambulatory peritoneal dialysis (CAPD) or predialysis), immunosuppression (cyclosporin or azathioprine and prednisolone), number of previous transplants and surgeon performing the transplant. The majority of kidneys were retrieved using *in situ* perfusion with no initial warm ischaemia (*Table 1*). PNF was defined as the need for dialysis in the first 7 days after transplantation.

All recipients were treated with perioperative antibiotics (2 g ampicillin, 2 g flucloxacillin and 500 mg ceftazidime) and steroids (methylprednisolone 500 mg intravenously at the time of the anastomosis, 24 h later and on postoperative days 5, 6 and 7 if no function) according to a standard protocol. All patients were nursed on an intensive care unit for 24 h and thereafter on a specialized transplant unit with a standard fluid balance policy attempting to maximize hydration of the patient. Cyclosporin was given orally pre-operatively at a dose of 15 mg kg^{-1} day^{-1}, this dose being reduced according to plasma trough levels (radioimmunoassay) to a mean of 10 mg kg^{-1} day^{-1} in divided doses by postoperative day 7.

Statistical analysis was performed using a stepwise logistic regression model and Mann–Whitney U, χ^2 and Kolmogorov–Smirnov tests.

Results

The overall PNF rate in this series was 57 per cent. The only variable found to have a significant independent positive association with PNF was the use of cyclosporin as an immunosuppressant (*Table 2*) ($\chi_1^2=4\cdot33$; $P=0\cdot04$). After allowing for the effect of cyclosporin, second warm ischaemia was significantly associated with PNF (*Table 3*) ($\chi_1^2=4\cdot72$; $P=0\cdot03$). PNF was not significantly associated with any individual surgeon, and was not significantly different in living

Table 1 *Frequency and results of variables studied ((mean ± s.d.) or median (range)*) in functioning and non-functioning kidneys*

Variable	Functioned *n* = 45	Non-functioned *n* = 61
Recipient BP (mmHg)	122/79 ± 17/12	114/75 ± 26/12
Recipient age (years)	40 ± 15	39 ± 15·7
Recipient sex		
Male	47 %	51 %
Female	53 %	49 %
Recipient urine output (ml)		
Zero output	36 %	33 %
Measurable output	570 (10–2000)*	570 (50–2000)*
Panel-reactive antibodies	40 %	40 %
Dialysis		
Haemodialysis	44·4 %	49·2 %
CAPD	55·6 %	47·5 %
Predialysis	0	3·3 %
Perfusate		
Collin's	77·8 %	67·2 %
Marshall's	11·1 %	14·8 %
Sach's	4·4 %	6·6 %
Citrate	6·7 %	11·5 %
Initial warm ischaemia (min)		
0	69 %	62 %
> 0	8·5 (2–29)*	5 (2–35)*
First transplant	86 %	77 %
Cold ischaemia (min)	1192 ± 469	1336 ± 511
Donor age (years)	34·8 ± 16	34·7 ± 16
Donor urine output (ml)	2958 (650–25 900)*	3360 (970–25 600)*
Donor BP (mmHg)	122/73 ± 33/13	121/74 ± 26/16
HLA mismatch (mean no.)	3·3	3·5

CAPD, chronic ambulatory peritoneal dialysis

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Table 2 *Factors individually related to primary non-function*

Factor		Function	Non-function
Cyclosporin*	Cyclosporin	36 (39%)	57 (61%)
	No cyclosporin	9 (69%)	4 (31%)
Second warm ischaemia†	< 30 min	30 (50%)	30 (50%)
	> 30 min	15 (33%)	31 (67%)

* $\chi_1^2 = 4{\cdot}33$, $P = 0{\cdot}04$; † $\chi_1^2 = 3{\cdot}22$, $P = 0{\cdot}07$

Table 3 *Combinations of factors and primary non-function (PNF)*

	SWI	No PNF	PNF	Total
No cyclosporin	< 30 min	3	2	5
	> 30 min	6	2	8
	Total	9	4	13
Cyclosporin	< 30 min	27	28 (51%)	55
	> 30 min	9	29 (76%)	38
	Total	36	57	93

SWI, second warm ischaemia

donor or cadaveric transplants. High percentages (> 75 per cent) of panel-reactive antibodies, and long first warm ischaemia times (> 10 min) were not positively associated with PNF. Results for other variables are shown in *Table 1*.

Discussion

Most groups in the transplant community worldwide have very similar 1-year graft function rates[11] despite a multitude of differing immunosuppressive regimens. However, 1-week graft function rates differ widely between centres, and the reasons for this remain unclear.

The implications of PNF in transplanted kidneys are not just limited to the long-term graft outcome[2,3]. A patient with transplant malfunction may require numerous investigations including invasive tests such as transplant biopsy. Dialysis may be required in the early postoperative period, with risks of haemorrhage, and hospital stay may be increased.

Many factors have been linked to PNF: cyclosporin[11], cold ischaemia > 30 h[4], number of previous transplants[2], donor age > 50 years[5], the use of Eurocollins or other perfusion solutions[6,13] and ice storage compared with pulsatile perfusion[7] or combined with it[12]. Some workers, however, have found pulsatile perfusion to be a causal factor in PNF[1] and have not found cyclosporin or cold ischaemia to be of relevance[2]. There is, thus, confusion in the literature as to what is of importance and what is not in PNF. Most studies have been retrospective or have looked only at a small number of variables. The only available controlled prospective data comes from animal work and it suggests that warm ischaemia and cyclosporin[8,9] synergistically damage kidneys. The use of calcium channel blocking drugs in the renal perfusate of donors is associated with a decreased incidence of PNF[10] and these drugs may protect renal tubular cells against the adverse effects of cyclosporin and the 'reperfusion injury'[14]. Interactions between cyclosporin, the prostaglandin system and post-ischaemic renal failure may also explain PNF[15,16]. Our data suggest that, independently or in combination, cyclosporin and a second warm ischaemia time of 30 min are associated with PNF of renal allografts. One possibility is that the starting dose of cyclosporin (15 mg kg^{-1} pre-operatively then 10 mg kg^{-1} daily for the first week) with pulses of methylprednisolone in the perioperative period could cause PNF. On the basis of cyclosporin levels, however, very few patients exhibited cyclosporin toxicity at this dose and 39 per cent of recipients receiving cyclosporin *did* have immediate function (*Table 2*). We recommend that where possible an anastomosis time of more than 30 min should be avoided or peranastomotic cooling of the kidney should be used. Care should be taken in the use of cyclosporin in the early postoperative period.

New drug protocols using 'low dose' (8 mg kg^{-1}) cyclosporin from the day of operation[17] in combination with azathioprine and prednisolone have shown as good 1-year graft survival as cyclosporin in a dose of 12 mg kg^{-1} with prednisolone. It is interesting that the early recommendations of caution with cyclosporin in the immediate post-transplant period[18] have now come full circle again, with some groups avoiding the drug at all times in the induction phase of immunosuppression and using it only for maintenance immunosuppression once initial graft function is established[19]. This 'sequential therapy' is now popular in several centres, particularly in the USA. Alternatives to limiting the use of cyclosporin in the early transplant period include graft reperfusion with a calcium antagonist. This can be done alone (100 mg l^{-1} diltiazem in 500 ml Eurocollins) just before transplant, or in combination with intravenous diltiazem given to the recipient[14]. The theoretical mechanism of action of this group of drugs is to prevent calcium influx into the renal cells at the time of reperfusion. Renal vasoconstriction is associated with acute renal failure, cyclosporin nephrotoxicity and PNF[20], and not surprisingly prostacyclin treatment of the donor (100 g bolus IV) and in the flush solution (100 g l^{-1}) has improved initial function rates[21]. Oxygen free radicals are released during reperfusion, and agents which scavenge these cytopathic complexes (e.g. iron-chelating substances such as desferrioxamine and caeruloplasmin) have been shown to decrease the perfusion injury in dogs[22].

The widely differing primary function rates between transplant groups are in contrast to the now excellent (of the order of 80 per cent) 1-year graft survival rates reported from most centres since the advent of cyclosporin. Whatever the underlying mechanisms are that regulate which kidneys function at once and which do not, we have found cyclosporin and a second warm ischaemia time of greater than 30 min to be associated with PNF. Apart from the possibility of a poorer longer term result, increased morbidity, hospital stay and investigations, the patient with delayed primary function is psychologically at a disadvantage when compared with his or her wardmate who has a falling serum creatinine the day after transplant.

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Case report

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Percutaneous obliteration of a chronic duodenal fistula

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We report the use of a percutaneous method to obliterate a chronic duodenal fistula arising after gastroduodenal surgery.

Case history

The 46-year-old patient was operated on in 1975 at another hospital for duodenal ulcer. He underwent truncal vagotomy and pyloroplasty. A few months later the ulcer recurred, and 5 years later revagotomy was performed, but failed to relieve his symptoms, and he was referred to our hospital in November 1980. Six months later an antrectomy was performed with a Billroth II Hofmeister–Finsterer type of reconstruction.

On day 15 after surgery, a small wound abscess was drained but discharge persisted; 9 months later the abscess was explored surgically and silk sutures were removed. In spite of this, the suppuration of the wound persisted. In July 1983, in view of the persistence of the cutaneous fistula, fistulography was performed and revealed a connection to the duodenal stump (*Figure 1*).

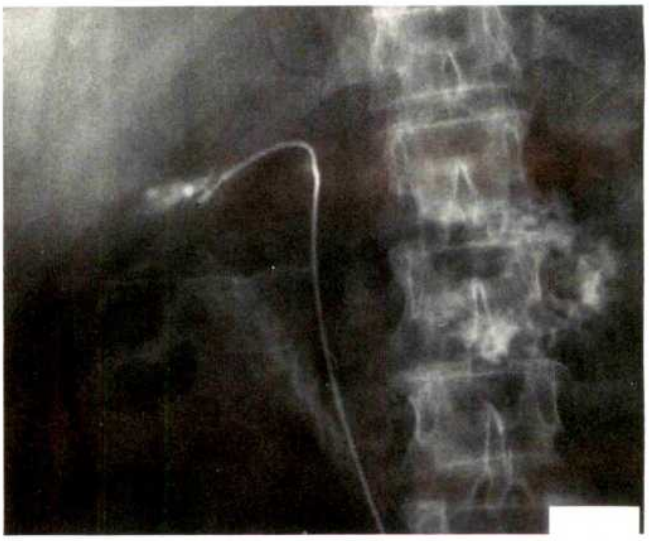

Figure 1 *Fistulous tract catheterization before ETHIBLOC® (Ethicon) injection*

In view of the complexity in resolving this duodenal fistula by surgical intervention, we attempted percutaneous obliteration: firstly by introduction of cyanoacrylate through a delicate polyethylene catheter. This was not successful because the cyanoacrylate adhered to the catheter, and was extracted on removal of the catheter.

We next attempted injecting prolamine (ETHIBLOC®), along the length of the tract through a fine catheter, with no apparent technical problems. Nevertheless, abundant biliary drainage appeared at the fistulous opening in subsequent days. We injected prolamine once more 8 days later, and the discharge stopped completely within 4 days.

The patient has experienced no relapse of the fistula during the 5 years after the procedure.

Discussion

Prolamine, an amino acid polymer, has been used to treat chronic pancreatitis[1] to obliterate the duct of Wirsung and in transplantation of the pancreas, with the intention of avoiding enteropancreatic anastomoses[2].

Sporadically, the medical literature carries articles describing patients who have been treated percutaneously for enteric fistulae. Recently, Marco *et al.*[3] published a case of obliteration of an oesophagobronchial fistula by injecting cyanoacrylate endoscopically. This substance was not useful in our patient, who presented a chronic fistula from the duodenal stump. In view of the complexity which the surgical treatment of this fistula would present, we used prolamine with excellent results.

Further experience with this technique may demonstrate that some types of chronic fistula, with limited flow, can be closed by percutaneous treatment with no morbidity and the avoidance of complex surgical interventions.

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Non-operative management of retroperitoneal fibrosis

It is generally recognized that in many patients the ureteric obstruction and other manifestations of non-malignant retroperitoneal fibrosis will respond to treatment with corticosteroids. However, most surgeons are reluctant to use steroids as the primary treatment for patients with this condition, mainly because of the risk of mismanagement of malignant retroperitoneal fibrosis. Our experience in the care of 17 patients with non-malignant retroperitoneal fibrosis has led us to believe that an initial non-surgical approach is both safe and preferable.

Keywords: Retroperitoneal fibrosis, benign, non-surgical, steroids

Many cases of idiopathic retroperitoneal fibrosis (RPF) can be treated without operation by means of corticosteroid therapy. Nevertheless, the current view is that in nearly all cases surgical ureterolysis is preferable in order to establish the diagnosis and as the primary form of treatment. Although ureterolysis is often successful in relieving ureteric obstruction, it may be complicated by recurrence and by ureteric leakage. Techniques for overcoming these problems have included omental wrapping of the ureter[1], ileal interposition[2,3], ureteric splinting[4] or stenting[5], wrapping the ureter in a Silastic tube[6], ureteric myotomy[7] and renal autotransplantation[5].

During the past 18 years we have managed most of our 17 cases of RPF without resorting to operation. The purpose of this paper is to present our experience of these patients and to propound the view that non-operative treatment should be considered more seriously in the management of RPF.

Patients

In an 18-year period (1968–86), 17 patients were diagnosed as having RPF at the North Staffordshire Hospital Centre, Stoke-on-Trent. These occurred in a population of about 500 000 and a study of hospital and post-mortem records has not revealed any other cases of RPF during this period. Fourteen of the patients have been treated primarily with steroids.

Clinical features

The salient features of each patient's clinical presentation and progress are shown in *Table 1*. Loin pain, sometimes severe enough to resemble renal colic although usually more protracted in nature, was a presenting symptom in seven. In five instances hydroceles were among the presenting features; these diminished in size on treatment of the RPF. Two patients had severe leg oedema at the time of presentation; in each case the oedema resolved on steroid therapy. In patients 14 and 17, RPF was diagnosed as a result of investigations undertaken to establish the cause of urinary frequency and sterile pyuria. These investigations included repeated urine cultures in order to rule out the diagnosis of urinary tract tuberculosis.

None of the patients gave a history of taking methysergide or of ingesting large quantities of analgesics. In patient 5, previous thyroid surgery had shown Riedel's thyroiditis. Patient 4 had undergone a right pneumonectomy 7 years previously for spontaneous mediastinal fibrosis. Re-examination of the mediastinal tissue showed fibrotic changes identical to those found in RPF.

Diagnosis

In patient 5, the diagnosis was confirmed when a biopsy was taken in the course of ureterolysis. In the others the diagnosis rested on the radiological findings, the absence of any other demonstrable primary renal disease or obstructive uropathy, the response to treatment and the absence during the follow-up period of any other lesion which could account for the renal tract findings.

The radiological abnormalities were those which are well-recognized in RPF, namely a smoothly tapering narrowing of the ureter usually in its middle third and often with deviation towards the midline, and proximal dilatation of the upper renal tract. These changes were shown on intravenous urography in those renal tracts where obstruction and loss of function was not severe and by retrograde or antegrade imaging of the obstructed ureter in the remainder.

Computerized tomographic (CT) scanning has proved very useful both in demonstrating the presence and extent of the retroperitoneal lesion, and in showing a reduction in the size of the lesion and in the degree of ureteric obstruction after treatment.

Although the erythrocyte sedimentation rate has initially been elevated in all patients in whom it was measured, it is not of course sufficiently specific to be of much diagnostic value. However, it would appear to be a useful measure of response to treatment. CT scanning was not available when patients 15 and 16 presented with lower limb oedema. In these patients venography and lymphography were used in order to make the diagnosis of venous thrombosis and to rule out other lesions such as retroperitoneal neoplasia.

Results

Management

Initial treatment is aimed at the correction of any serious electrolyte or fluid balance problems and dealing with hypertension if present. In one instance peritoneal dialysis was used but the relief of complete upper tract obstruction is best achieved by means of percutaneous nephrostomy. We feel that this has the advantage over ureteric catheterization or stenting because evaluation of the response to treatment is easily achieved by descending ureterography and clamping of the tube, which can be removed as soon as the ureter is found to be patent.

Only three patients have not been given steroid treatment (2, 6 and 7). Each of these responded to the correction of fluid balance problems and treatment of hypertension. Although the initial episode of illness in patient 4 was dealt with satisfactorily without using steroids, at a subsequent episode 11 years later steroid therapy was introduced.

In the remaining 13 patients, steroids were given as a primary form of treatment, the first dose of prednisolone varying from 30 to 60 mg daily. The tendency has been to use a larger dose in more seriously ill patients, reducing the dose as soon as a response is evident. In our experience, the ureteric obstruction is usually relieved within 7–10 days. This response may be assessed by descending ureterography, intravenous urography, or by CT scanning. Equally valuable evidence of response is relief of symptoms and a fall in serum creatinine in patients where the level is initially elevated.

The dose of prednisolone was usually reduced to 5–10 mg daily over a period of a few weeks and usually maintained at this level for at least 2 years. Discontinuation of prednisolone in patients 1 and 13 after 3 months and 1 year, respectively, did not lead to any problems, whereas patient 5 was treated for 1 year and then suffered a return of her symptoms and signs of renal failure after 2 years without steroids. Since there was some

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Table 1 *Features of clinical presentation and progress in 17 patients with non-malignant retroperitoneal fibrosis*

Case number	Age at presentation (sex)	Mode of presentation	Serum creatinine (μmol/l)	Diagnostic criteria	Method of treatment	Response to treatment			Duration of follow-up (years)	Comments	Condition at follow-up
						Subjective	Objective	Serum creatinine (μmol/l)			
1	36 (F)	Abdominal pain and anuria	886	IVU, CT, RUG, ESR 100	T-tube ureterostomy, steroids for 3 months	Symptom-free	CT: improved, ESR 7	106	2		Alive and well
2	74 (M)	Confusion and renal failure	369	IVU, RUG	Peritoneal dialysis, hypotensive drugs	Symptom-free		180	9		Alive and well
3	59 (M)	Renal failure, bilateral hydroceles	1186	IVU, RUG, ESR 46	Control of fluid balance	Little	ESR 42	235	6	On low dose steroids at death	Died (carcinoma of stomach)
					Steroids	Symptom-free	ESR 1	117			
4	43 (M)	Renal failure, hypertensive encephalopathy	(Urea 21·1 mmol/l)	RUG, ESR 70, BP 200/120	Control of fluid balance, hypotensive drugs	Symptom-free	IVU: improved, ESR 10, BP 150/190	(Urea 10·2 mmol/l)			
	54	Renal failure, hypertension, right hydrocele	830	CT, US ESR 17 BP 170/100	Percutaneous nephrostomy, steroids	Symptom-free	CT: improved, ESR 10, BP 160/90	290	15	On low dose steroids at death	Died (myocardial infarction)
5	48 (F)	Backache, renal failure	725	IVU, RUG, ESR 54	Steroids for 1 year	Symptom-free	IVU: improved, ESR 5	132			
	51	Backache, renal failure	614	AGU, biopsy, ESR 39	Ureterolysis, steroids	Symptom-free	Improved on US, ESR 4	112	8	On low dose steroids	Alive and well
6	63 (M)	Renal impairment, hypertension, hydroceles	360	Bil. RUG	Hypotensive drugs, diuretics	Symptom-free	Nil	355	11		Died (carcinomatosis, primary site unknown)
7	65 (F)	Left loin pain, renal impairment	207	IVU, Bil. RUG, ESR 87	No specific treatment	Symptom-free	IVU: improved, ESR 15	131	3	Grossly obese	Died (pulmonary embolism)
8	46 (M)	Severe back ache, abdominal pain	703	CT, ESR 98	Steroids	Symptom-free	CT: improved, ESR 5	84	1	On low dose steroids	Alive and well
9	71 (M)	Loin pain, anorexia and weight loss, renal failure, aortic aneurysm	798	IVU, US, CT, ESR 141	Steroids	Symptom-free	CT: improved, ESR 45	136	2	Still on low dose steroids (creatinine 131, ESR 24)	Alive and well

10	61 (M)	Anaemia, renal failure, aortic aneurysm	666	US, CT, ESR 68	Steroids	Symptom-free	CT: improved, ESR 45	296	4	Deterioration in renal function led to increased dose of steroids	Alive and well
11	64 (M)	Renal failure, aortic aneurysm	1276	IVU, CT, ESR 79	Percutaneous nephrostomy, steroids	Symptom-free	CT: improved, ESR 13	274	2	Treated for diabetes (? steroid induced). Still on low dose steroids	Alive and well
12	42 (M)	Severe right loin pain	136	IVU, RUG, CT, ESR 35	Steroids	Symptom-free	IVU: normal, ESR 2	82	1	On low dose steroids	Alive and well
13	50 (M)	Severe left loin pain, bilateral hydroceles	125	IVU, RUG, ESR 45	Steroids for 1 year	Symptom-free, hydroceles smaller	IVU: normal, ESR 8	90	10	Now off steroids	Alive and well
14	59 (M)	Frequency of micturition	155	IVU, RUG, CT, ESR 30	Steroids for 2 months	Symptom-free	IVU: unchanged, CT: some improvement, ESR 9	141	3	Operation advised (patient refused). Off steroids	Alive and well (creatinine 75)
15	62 (M)	Left femoral vein thrombosis, left hydrocele	120	IVU, RUG, ESR 70	Steroids	Symptom-free	IVU: normal, ESR 39	96	9	Still on low dose steroids	Alive and well (ESR 11)
16	73 (M)	Backache, IVC thrombosis	150	IVU, RUG, ESR 52	Steroids	Symptom-free	IVU: unchanged, ESR 4	136	9	Still on low dose steroids	Alive and well
17	70 (M)	Frequency of micturition	101	IVU, CT, ESR 29	Steroids	Still has frequency	IVU: normal, ESR 2	93	0·75	Still on low dose steroids	Alive and well

AGU, antegrade ureterography; IVU, intravenous urography; RUG, retrograde urography; CT, computer assisted tomography; IVC, inferior vena cava; ESR, erythocyte sedimentation rate; BP, blood pressure; US, ultrasound scan

doubt as to the diagnosis in this patient, it was confirmed by open biopsy and ureterolysis was performed, followed by steroid therapy. In other patients the discontinuation of steroid therapy has resulted in deteriorating renal function or a return of symptoms so that prolonged treatment has been necessary.

This lack of any consistent pattern emphasizes the need for careful long-term follow-up. At least one follow-up CT scan is useful in order to assess the size of the retroperitoneal lesion and the degree of upper tract dilatation, but for most routine purposes ultrasound scanning and measurement of the serum creatinine and the ESR will suffice.

Progress and follow-up

Treatment resulted in symptomatic improvement in all patients. Renal function has at best improved dramatically, or at worst has been maintained. The degree of radiographic improvement has varied, in some patients the upper renal tracts returning to normal, or near-normal, whereas in a few radiological improvement has been less striking, despite a fall in the serum creatinine.

Discussion

The main disadvantage of the non-operative management of patients with presumed RPF is the lack of histological proof of the diagnosis. In those series where exploration has been routine the most common cause of diagnostic error has been the existence of a retroperitoneal malignancy. Webb and Dawson-Edwards[8] found 3 malignant cases in a series of 16 but Koep and Zuidema[9] reviewed 481 patients with RPF from the literature and noted that malignancy was present in only 7·9 per cent. They state that the diagnosis of malignancy at operation is not necessarily easy; in some cases the initial biopsy led to a diagnosis of benign RPF whereas subsequent biopsy or autopsy examination revealed malignancy. They stress that multiple deep biopsies are necessary for histological certainty and that frozen section diagnosis is not entirely reliable. Nitz *et al.*[10] analysed the results of treatment of four patients in whom a retroperitoneal malignancy was masquerading as benign RPF. Koep and Zuidema[9] also note the association of RPF with inflammatory diseases such as Crohn's disease and diverticulitis.

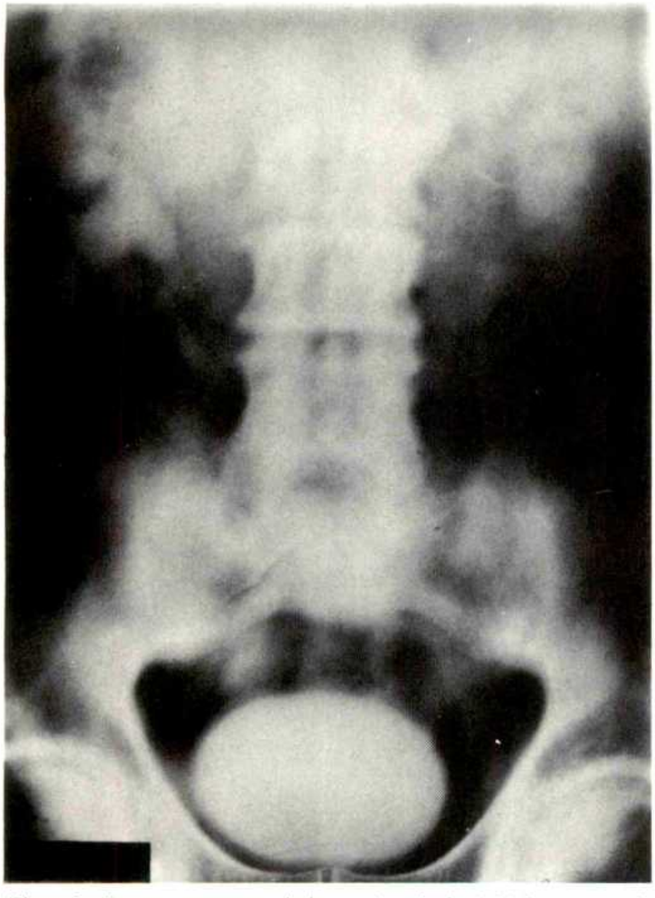

Figure 1 *Intravenous urograph from patient 3 after initial treatment of renal failure but before steroid treatment. Very little contrast is seen on the left side, but the right upper tract is dilated*

Surgical treatment is not without hazard. Tiptaft *et al.*[11] treated 24 patients with 1 postoperative death (myocardial infarction) and 3 patients later developed intestinal obstruction. Three of their patients had postoperative leakage from the ureter. Mundy *et al.*[12] list 67 postoperative complications in 36 patients, mostly related to hypertension and thrombo-embolism in the postoperative period. Urinary fistula occurred in seven and in the follow-up period one patient died as a result of obstructive uropathy; seven other patients died in the follow-up period, four from causes attributable to hypertension. Other authors have also noted a high incidence of postoperative complications and recurrence[4,5,7,13,14].

To quote Tiptaft *et al.*[11], who advocate ureterolysis and omental wrapping, 'this is a considerable operation and it is not surprising that there have been operative and post-operative complications'. This statement would seem to hold good whatever surgical technique is used.

Our experience suggests that patients with RPF can be divided into two fairly well defined groups.

The first group contains the most seriously ill and are those with varying degrees of renal impairment sometimes extending to oliguria or anuria. It seems likely that the onset of the fibrosis in these patients is insidious and that by the time of presentation the fibrosis is established as is some degree of irreversible renal impairment. It is probably in these patients, who have a poor response both to operation and to steroids, that the correction of fluid balance problems and the treatment of hypertension is most important. This possibility of improvement in renal function occurring as a result of general medical measures has also been noted by Mahoney and Edwards[19] in two patients and by Tiptaft *et al.*[11] in one. However, although attention to fluid balance and blood pressure problems is needed in all cases it is clear that most will require more radical treatment, namely steroids (*Figures 1* and *2*), surgery or a combination of these.

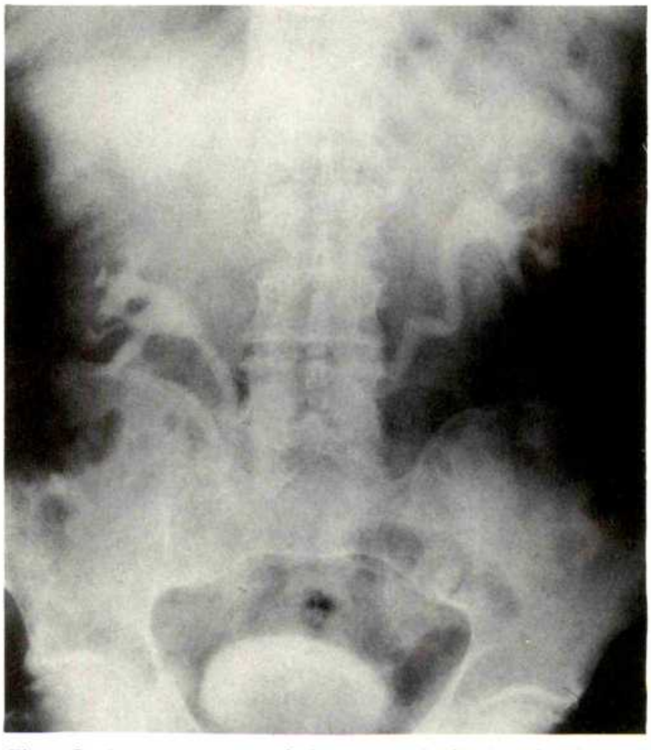

Figure 2 *Intravenous urograph from patient 3 after 3 weeks of steroid treatment. Left upper tract is now well shown and the right upper tract is less dilated*

The second group of patients consists of the less seriously ill (12–17 in *Table 1*) and are those who present, presumably at an earlier stage of the disease, sometimes with loin pain, hydrocele or venous thrombosis but sometimes with non-specific symptoms such as frequency of micturition. In these cases the ureteric obstruction is predominantly unilateral.

In three of our patients aneurysmal dilatation of the aorta was present although in none was surgical intervention indicated. The association of aortic aneurysm and RPF is well-recognized[15,16] as is the fact that many of these cases can be managed on steroid therapy[17]. Darke *et al.*[18] found that even in the presence of dense perianeurysmal fibrosis there is still a risk of aortic rupture. Despite these differing presentations, there is no convincing evidence of a relationship between the stage of the disease and the histological appearance[7].

Ross and Tinkler[20] and Hawk and Hazard[21] reported the use of corticosteroids to treat idiopathic RPF but most authors have preferred to reserve steroid therapy for patients in whom surgical treatment has failed, for relapses after surgery or for cases where the diagnosis is reasonably certain but the patient is thought to be unfit for operation. Serious side-effects of prednisolone have been recorded by Tiptaft *et al.*[11], namely pathological fractures in osteoporotic vertebrae necessitating withdrawal of treatment, and by Mitchinson *et al.*[22] In one of their patients the development of mental disturbance led to withdrawal of prednisolone. However, it is not so much the fear of side-effects that has led most authors to avoid the use of corticosteroids as a primary form of therapy as the risk of making the wrong diagnosis, particularly the risk of missing a retroperitoneal malignancy. We believe that if the available modern diagnostic techniques are carefully applied this risk can be reduced to a minimum and that, in any event, a short delay in the diagnosis of malignancies of this nature will make little difference to the outcome. The suggestion made by Charlton[23], that a biopsy be used to confirm the diagnosis before instituting steroid treatment sounds attractive but, as was noted by Koep and Zuidema[9], this approach may be fallible in that malignant areas may be missed. Kerr *et al.*[14] point out that there are inherent dangers in taking deep biopsies from retroperitoneal tissues, particularly in respect of damage to the major vessels.

Our interpretation of the literature suggests that the risks associated with surgical treatment and the likelihood of subsequent relapses necessitating further surgical intervention are relatively high. In contrast the present study suggests that non-operative management is preferable, so long as the diagnosis has been established with near-certainty and that failure to respond within a period of 2 to 3 weeks is considered an indication for open operation.

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Improvement of renal function in azotaemic hypertensive patients after surgical revascularization

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Between 1974 and 1986, 17 patients (16 men and 1 woman) with renal insufficiency (serum creatinine >1·5 mg/dl, mean 3·75 mg/dl), with a mean age of 51·3 years, underwent surgical renal revascularization. Two of them were on maintenance haemodialysis. All were severely hypertensive in spite of antihypertensive drugs. Atherosclerosis was the cause of renal stenosis in 14 cases and fibromuscular dysplasia in 3. Operative procedures included splenorenal shunt (5), autotransplantation (3), aortorenal bypass (3), hepatorenal bypass (1), bilateral renal endarterectomy (1), renal ostial closure (1) and nephrectomy (3). Mean serum creatinine showed a decrease from 3·76 to 1·65 mg/dl ($P<0.005$). Mean arterial pressure dropped from 161 mmHg to 103 mmHg ($P<0.001$). Systolic and diastolic pressures also showed significant decreases. Two patients died. Four patients required a second operation and the renal function and blood pressure then improved. Renovascular disease must be ruled out in patients with renal insufficiency associated with hypertension, including those patients on haemodialysis. We conclude that renal revascularization surgery is a reliable and efficient form of treatment in selected cases of renal failure of renovascular origin.

Keywords: Renal function, azotaemic hypertensive patients, renal surgical revascularization

Most patients undergoing renal revascularization are operated upon for refractory renovascular hypertension. Today, this is a widely recognized curable form of hypertension and surgical results are usually good, with regression of hypertension to normal values, reduction of medication and improvement in the quality of life[1,2].

Renal insufficiency is mostly seen when dealing with renovascular hypertension in elderly patients with atherosclerotic renal artery disease. However, attention has not routinely been drawn to the azotaemia associated with renovascular hypertension. Following the initial report by Morris *et al.* in 1962[3] describing eight azotaemic patients who underwent renal revascularization, a few authors have reported encouraging experience of the aggressive surgical management of patients with severe azotaemia associated with hypertension[4–7].

Percutaneous transluminal renal angioplasty has recently emerged as a potential therapeutic alternative in the treatment of patients with renovascular disease[8–10]. The highest success rates have been reached in patients with fibromuscular dysplasia. Atherosclerotic involvement seems to be less responsive to this therapy[11]. Nevertheless, surgery still represents a valuable means of revascularizing the underperfused kidney. In this report we wish to present our experience in the surgical treatment of renal insufficiency associated with refractory renovascular hypertension.

Patients and methods

Between 1974 and 1986, 17 patients with documented renal insufficiency (serum creatinine >1·5 mg/dl) and refractory renovascular hypertension have been studied and surgically treated in our unit.

There were 16 men and 1 woman; their ages ranged from 38 to 69 (mean 51·3) years. Pre-operative serum creatinine ranged from 1·7 to 10·4 mg/dl with a mean of 3·76 mg/dl. Two patients were undergoing haemodialysis at the time of diagnosis and surgery. Pre-operative blood pressures ranged from 170 to 300 mmHg systolic to 95–160 mmHg diastolic. Mean arterial pressure was 161·18 mmHg. All patients had previously been placed on multiple antihypertensive agents including β-blockers, diuretics, calcium channel blockers, α-methyldopa and ACE inhibitors.

Fourteen patients had atherosclerotic renal artery disease and three had fibromuscular dysplasia. Unilateral renal artery stenosis was seen in seven patients, bilateral in six and renal artery thrombosis in four patients (*Table 1*). The two patients on haemodialysis and an additional patient with a serum creatinine of 6·6 mg/dl underwent renal biopsy before surgery. Viable renal parenchyma was observed.

Renal angioplasty

Four patients had previously undergone percutaneous transluminal renal angioplasty but this was unsuccessful in all because of the inability to dilate the stenosis.

Operative treatment

Five patients underwent splenorenal shunt, three autotransplantation, two unilateral aortorenal bypass, one bilateral aortorenal bypass, one hepatorenal bypass, one bilateral renal artery endarterectomy and one closure of the renal artery ostium. Three patients underwent nephrectomy. Because of other vascular conditions, associated procedures were performed, including four cases of bifurcated aortofemoral Dacron (E. I. Dupont de Nemour Inc.) graft and one case of straight Dacron tube interposition in the abdominal aorta.

Table 1 *Patient details*

Aetiology	Unilateral stenosis	Bilateral stenosis	Thrombosis	Total
Atherosclerosis	5	5	4	14
Fibromuscular dysplasia	2	1	—	3
Total	7	6	4	17

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Table 2 *Results after revascularization*

	Pre-operative	Postoperative	P
Creatinine (mg/dl) (mean)	3·76	1·65	<0·005
Systolic BP (mmHg)	229·70	138·23	<0·001
Diastolic BP (mmHg)	128·82	83·52	<0·001
Mean BP (mmHg)	161·18	102·96	<0·001

BP, blood pressure

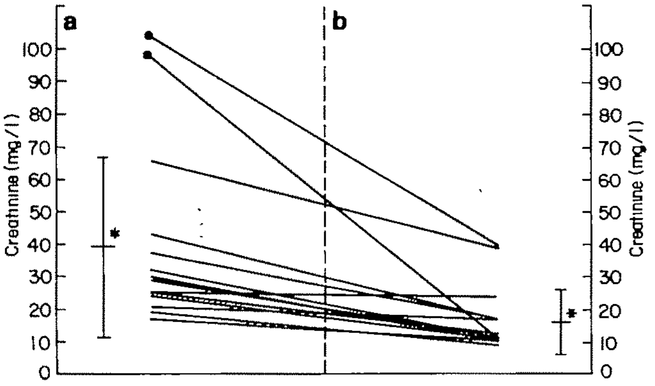

Figure 1 *Changes in renal function after revascularization surgery* (**a** *before;* **b** *after surgery*). * P<0·01; ●, *patients on haemodialysis*

Results

Serum creatinine

The mean pre-operative serum creatinine level of 3·75 mg/dl dropped to 1·65 mg/dl, a statistically significant improvement ($P<0·005$) (*Table 2*). Renal function initially improved in all patients; however, four patients showed no change or worsening in renal function, together with persistent hypertension, and required a second surgical procedure. The two patients on pre-operative maintenance haemodialysis never required it after surgery (*Figure 1*). Thus, 76 per cent of patients improved.

Blood pressure

The mean pre-operative blood pressure showed a decrease from 161·2 mmHg to 103·0 mmHg postoperatively ($P<0·001$). Thirteen patients (76 per cent) improved and four showed no change or worsened (*Figure 2*).

Second operation

Four patients were reoperated upon because of impaired renal function and/or persistent hypertension. Two patients were reoperated upon early (less than 1 month) and two late (12 and 7 months) after surgery. All had thrombosed grafts. Second procedures included one hepatorenal bypass, one left femoral Dacron graft-to-renal artery bypass and right nephrectomy, one case of takedown of an infected splenorenal shunt and one case of autotransplantation.

Hospital mortality

There have been two cases of in-hospital mortality (12 per cent). One of the patients died after the reoperation performed during the same admission. Both these patients died from multisystem failure and massive bowel infarction.

Patients on haemodialysis

Good results were achieved in the two patients undergoing haemodialysis at the time of surgery. One of them, with a pre-operative serum creatinine of 9·8 mg/dl, is doing well, and creatinine is currently 0·8 mg/dl, 31 months after the operation. The remaining patient showed a drop in serum creatinine from 10·4 to 4·0 mg/dl, 7 months after a saphenous vein hepatorenal bypass. However, this graft thrombosed 9 months after surgery. Autotransplantation of the right kidney was performed and the serum creatinine is now 4·0 mg/dl, and the patient does not need haemodialysis.

Follow-up

Follow-up ranges from 8 to 150 months with a mean of 43·4 months. One patient, who required bilateral renal artery endarterectomy, was lost for follow-up at the 24th postoperative month. No cases of late mortality have been recorded.

Discussion

Renovascular hypertension is the commonest form of curable hypertension[7] and is particularly amenable to surgical treatment. Percutaneous transluminal renal angioplasty has recently been considered as an alternative therapy for renovascular disease, especially in the cases of fibromuscular dysplasia[9–12] where it should be considered the first line of treatment. The good results recently presented by Miller *et al.*[12] in a comparative study which included 102 patients seem to support this statement. In the series presented here, the results of surgery have been gratifying in relation to both renal failure and hypertension: 75 per cent of the patients were improved or cured.

Several authors have focused attention on the surgical treatment of renal failure associated with hypertension of renovascular origin[4–7,13–15]. Renal biopsy is thought to be a significant diagnostic tool in addition to isotopic scanning, trying to ascertain the amount of viable parenchyma, especially in cases of advanced chronic renal failure and kidneys less than 9 cm in size. Renal biopsy is particularly helpful because it helps to define the indication for surgery. We consider a kidney to be unsalvageable when 20 per cent or more glomeruli are obliterated by fibrous proliferation.

In view of the renal insufficiency reported before surgery, surgical results are encouraging[13,15,16]. In our series renal function initially improved in all patients; however, four patients later showed a new increase in serum creatinine levels and reoperation was indicated because of the suspicion of graft dysfunction. Therefore, 13 patients (76 per cent) showed initial improvement and all returned to near normal life with minimal

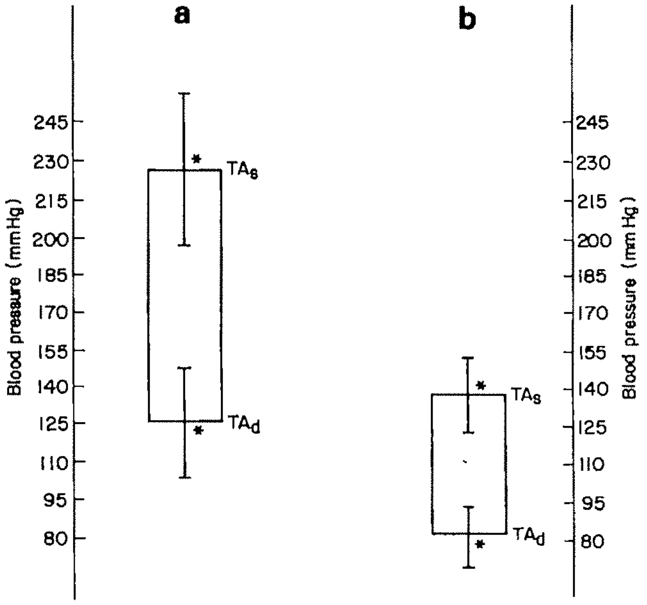

Figure 2 *Changes in blood pressure after surgical therapy* (**a** *before;* **b** *after surgery*) * P<0·001, *pre-operative versus postoperative blood pressure; TA$_s$, systolic blood pressure, TA$_d$, diastolic blood pressure*

or no medication. The three survivors after reoperation are currently doing well and no further renal failure has been detected.

Having in mind our experience and that of others, we consider the indications for surgical renal revascularization to be:

(1) Refractory renovascular hypertension after multiple antihypertensive agents or unsuccessful transluminal angioplasty.
(2) Chronic renal failure of renovascular origin with viable renal parenchyma on biopsy (80 per cent or more functioning glomeruli, size >9 cm, a collateral circulation, and good distal arterial bed) and haemodialysis patients with renovascular disease and a viable kidney.

Some authors have noted that nephrectomy must be considered only as a last resort in the treatment of renovascular disease[15-16]. Renal biopsy helps in defining which patients should undergo primary nephrectomy. When reconstruction is feasible, aortorenal bypass is the preferred surgical option[15]. However, failure of a previous aortorenal graft and extensive abdominal aortic and iliac atherosclerosis can preclude the construction of such aortorenal grafts. In such cases, other types of reconstruction must be used. The use of the hepatic circulation for management of right renal artery disease has been advocated by Libertino *et al.*[17] and others[18-19] with encouraging results. Splenorenal shunt and other types of extra-anatomical renal artery bypass should also be considered in this setting[18-20].

In conclusion, we believe that renovascular disease must always be sought in patients with renal insufficiency associated with arterial hypertension, including those patients on haemodialysis. Renal biopsy currently has an important role in defining the indication for surgery. Surgical treatment has demonstrated its reliability and efficacy in the management of renal insufficiency of renovascular origin in such selected patients.

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Separation of malignant cells during autotransfusion

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Autologous blood transfusion has been proposed to prevent the transmission of human immunodeficiency virus (HIV)[1]. Furthermore, it avoids the immunosuppressive effects of third party blood transfusion which, in patients undergoing surgery for malignancy, has been shown to be associated with a higher rate of recurrence of cancer[2]. One form of autotransfusion uses the Haemonetics Cell Saver (HCS) which transfuses back into the patient resuspended red blood cells (RBCs) which have been filtered and washed after suction retrieval from the operation site. Autotransfusion of this type reduces the requirement for bank blood[3]. The application of this technique may be limited by the assumption that tumour cells will be retrieved and resuspended with red blood cells and subsequently infused into the patient. We therefore performed an experiment to determine whether tumour cells in blood processed by the HCS were resuspended with the red blood cells or discarded with the waste.

Materials and methods

Two human tumour cell lines were used. SC[4] is an EBV-transformed lymphoblastoid cell line growing in continuous culture and this was used in the exponential phase. Cells were incubated with 800 μl chromium 51 (3.3 mCi/ml) for 60 min at 37°C, then washed twice, and resuspended in tissue culture medium, and $4\cdot6\times10^{7}$ cells were added to each unit of blood. The second cell line, HT29[5], is a human adenocarcinoma which was passaged in nude mice, the tumour excised and disaggregated by mechanical shear and protease digestion. Cell population numbers were counted and the tumour population checked by flow cytometry. This showed that 42 per cent of the cells were HT29 tumour cells, and 58 per cent were mouse stromal cells. Cells were incubated with 200 μl chromium-51 (3.3 mCi/ml) for 60 min at 37°C, were then washed twice and resuspended in tissue culture medium, and 5×10^{6} labelled cells were added to each unit of blood.

Each experiment was performed in duplicate. Samples of blood were taken before the addition of the labelled tumour cells for baseline measurement in the scintillation counter. After the labelled tumour cells had been added to the blood it was thoroughly mixed and further samples of blood were removed. Each unit of blood was then processed through the cell saver and the red cells were resuspended on each occasion in 460 ml normal saline to a haematocrit of 55 per cent, there being 1750 ml in the discarded wash on each occasion. Further samples from the processed and resuspended blood cells were taken and equal volume samples from the waste were also collected; all samples were taken in triplicate. On each occasion further triplicate samples were taken for centrifugation to separate cells from the serum or resuspension solution; red blood cell fraction and sera or resuspension samples were then individually counted so that not only total ^{51}Cr but that within cells and free isotope could be measured. Samples were counted in a Hewlett Packard Autogamma Scintillation Spectrometer 5360.

Results

The results are shown in *Table 1* and expressed as counts per minute after subtraction of background levels.

Table 1 *Distribution of labelled tumour cells added to whole blood, before and after processing in the cell saver*

	Experiment 1 SC	Experiment 2 HT29
Before processing		
Whole blood	45650 ± 944	3662 ± 219
RBC fraction	35116 ± 580	3154 ± 149
Sera fraction	8042 ± 836	569 ± 92
After processing and resuspension in normal saline		
Resuspended RBCs	41624 ± 1452	3080 ± 217
RBC fraction	39644 ± 1514	2409 ± 202
Normal saline fraction	1048 ± 86	310 ± 18
Waste (washings)	2448 ± 264	291 ± 14

Values are mean counts per min ± s.e.m

Before processing the ^{51}Cr is mainly in the RBC fraction and thus the isotope is within the tumour cells in this fraction and only a small amount of free isotope is present in the sera. After processing again the majority of the ^{51}Cr is in the RBC fraction and only a small amount of isotope in the resuspension fluid, furthermore the level of counts is low in the waste (washings).

These findings indicate that the tumour cells containing the ^{51}Cr separate with the resuspended red blood cells, and that the tumour cells are viable as only a small amount of isotope has leaked into the resuspension fluid or washings.

Discussion

These results demonstrate that when blood containing tumour cells is processed by the HCS the tumour cells are resuspended with the red blood cells and would be reinfused into the patient. The HCS separates the denser nucleated white cells of the buffy coat from the non-nucleated red blood cells by centrifugation. It is therefore surprising that this did not occur with the nucleated tumour cells. It could be argued that this is because they are cell lines grown *in vitro*; however, whereas the SC cell line was grown entirely *in vitro*, HT29 was passaged through nude mice and therefore was grown *in vivo* before the experiments.

Tumour cells returned in this way may originate either directly from the tumour at the time of operation or indirectly from the circulation in which they have previously been disseminated. Those using the HCS in tumour surgery should be aware that malignant cells may be reinfused into the patient.

Acknowledgements

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Experience with percutaneous aspiration of amoebic liver abscesses

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Diagnostic aids such as CT scan[1], ultrasound[2], liver scintigraphy[3] and selective angiography[4,5], have made the diagnosis and treatment of liver abscesses easier and more precise in developed countries. In third world countries most of these ancillary services are usually not available and reliance on basic clinical methods is necessary. This paper reports experience of 16 cases of amoebic liver abscesses managed by repeated percutaneous aspiration and surgical exploration.

Patients and methods

From January 1982 to December 1986, patients suspected on clinical grounds of having a liver abscess or so called 'amoebic hepatitis' were placed on double therapy consisting of 800 mg metronidazole and 250 mg tetracycline orally every 8 h for 10 days. Most patients responded to this regimen and were discharged home to be followed at the medical out-patients' clinic. Those who did not respond or became worse were referred to the author for liver aspiration or open biopsy.

Investigation of such patients included postero-anterior and lateral chest X-rays, complete blood count, platelet count, stool and urine analysis as well as serum bilirubin. The liver size, consistency and area of maximal tenderness or elevation above skin level were determined.

At the bedside, under sterile technique, the skin was prepared and draped to expose only the point of maximal liver tenderness or elevation. An area of about 1·5 cm^2 skin overlying that point was infiltrated with 1 per cent Xylocaine (Astra Pharmaceutical Company Ltd., UK) using an 18 gauge needle. The infiltration was carried deep into the liver with intermittent aspiration until pus was obtained. At this point the needle was removed and a size 16 gauge venous cannula was introduced into the abscess cavity. The plastic cannula could be advanced further or its direction changed to ensure complete or near complete aspiration. Two samples of the terminal aspirates were sent for Gram stain, culture and sensitivity as well as histological studies.

Results

Sixteen patients suspected of having liver abscesses had repeated percutaneous cannula aspiration of their abscesses with excellent results in 15. The other patient had initial good response but was re-admitted 3 weeks after discharge with an acute abdomen found on exploration to be due to a partial free peritoneal rupture of a missed second amoebic liver abscess located on the inferior surface of the caudate lobe of the liver. He did well following wide deroofing and external drainage.

The quantity of pus obtained from the 16 patients treated by repeated percutaneous aspiration ranged from 50 to 5700 cm^3 with an average of 1425·7 cm^3. The average number of times each patient was aspirated was two. Three patients required only one aspiration while two patients required three and four aspirations at intervals of 5 days. The pus was sterile in 13 patients, *Staphylococcus aureus* organisms were isolated from two cases and streptococci in another two. *Entamoeba histolytica* cysts were isolated in only four instances.

Discussion

Amoebic liver abscesses are seen in younger age groups in Rivers State of Nigeria. This report shows that the abscesses can be effectively treated by repeated percutaneous aspiration combined with metronidazole and antibiotics if diagnosis is made early and drainage started before complications occur. McFadzean *et al.*[6], in 1953, treated 14 cases of pyogenic liver abscesses by repeated percutaneous aspiration and antibiotics instillation without mortality. Sheinfeld *et al.*[1], reporting their experience with six cases of pyogenic liver abscesses treated by continuous percutaneous catheter drainage, compared the results of various drainage procedures reported in the literature over a 10 year period. Their review showed clearly the superiority of repeated percutaneous aspiration or continuous transcutaneous catheter drainage over those of open surgical drainage with a mortality rate of 1·5 per cent as against 30 per cent. The present report reveals similar findings with no mortality and no discernible complication for 15 cases treated by repeated percutaneous cannula aspirations.

Our concern therefore is how to make early diagnosis and commence aspiration before complications of liver abscesses occur. Early and accurate diagnosis has been made possible in the developed countries by the availability of such diagnostic aids as ultrasound[2], liver scintigraphy[3], angiography[4,5], and computerized tomographic scanning (CT scan). Sheinfeld *et al.*[1] also found CT scanning helpful in their choice of percutaneous instead of open surgical drainage for their six patients.

Another issue is whether these 16 cases were of amoebic origin for the purpose of comparison. None of our patients had evidence of recent or concurrent infection elsewhere. No patient was receiving or received chemo-immuno- or radiation therapy; and none was immunocompromised. An indirect haem-agglutination amoebiasis reagent (IHA) test[7] carried out in two patients in this report was positive but in neither of these two cases were amoebic cysts recovered. Unless one actually recovers *E. histolytica* cysts from the abscess or liver tissue, it is not easy to categorize a liver abscess conclusively as amoebic. The fact that all the patients in this study except one had single large abscesses, as well as the good response to the treatment, make one conclude that these were all amoebic liver abscesses with secondary infection in four instances.

It is concluded that clinical assessment supported by chest radiography can give sufficiently accurate assessment of amoebic liver abscesses to allow percutaneous drainage.

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Conservative management of perforated duodenal ulcer

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The accepted therapeutic options in perforated duodenal ulcer are simple closure or immediate definitive operation. Conservative treatment, originally proposed by Wangensteen, was recommended as the treatment of choice in perforated acute duodenal ulcer by Taylor in 1956[1]. Today it is reserved for patients considered to be too ill to stand the stress of surgery or for situations where immediate surgery is unavailable. A trial of conservative management in all cases of perforated duodenal ulcer meeting the inclusion criteria was undertaken. Its efficacy and long-term outcome have been assessed.

Patients and methods

All 49 patients admitted under 1 surgeon (C.McC.) with a perforated duodenal ulcer from January 1968 to December 1985 were reviewed, the clinical details are shown in *Table 1*. Forty-eight patients were diagnosed by history and clinical examination, one at laparotomy. In all, 31 (63 per cent) had radiological evidence of perforation, a further 11 had evidence of perforation at immediate or subsequent surgery. The final six patients with normal serum amylase levels and not undergoing surgery had active or healing duodenal ulceration on subsequent barium or endoscopy studies without other pathology. Inclusion criteria consisted of a clinically diagnosed perforation of <9 h duration and a stable haemodynamic condition.

Conservative management entailed intravenous analgesia, antibiotics and rehydration. A large bore (18 French) radio-opaque nasogastric tube was passed to empty the stomach. Half hourly aspiration and free drainage for 12 h, extending to hourly aspiration with improvement, was commenced. Accurate tube placement in the distal greater curve and frequent re-assessment are mandatory in this regimen. Conservative treatment was abandoned if the patient failed to improve or deteriorated (increasing tachycardia, pyrexia, abdominal distension or pain).

Results

Seven patients failing to meet the inclusion criteria underwent immediate surgery: six had perforated over 12 h before presentation, the seventh was diagnosed at laparotomy. A total of 42 patients entered a trial of conservative therapy and 34 were successfully managed. The median duration of treatment was 4 days. Eight patients failed to improve and underwent laparotomy.

There were no significant differences between the failure group (although consisting of only eight patients) and the successfully managed group regarding age (unpaired Student's *t* test), duration of perforation before presentation (Mann–Whitney (2-tailed) *U* test), medications or length of ulcer symptoms (Fisher's exact test). Conservative treatment did not prolong hospital stay (*Table 2*).

Table 1 *Clinical characteristics of 49 patients with perforated duodenal ulcer*

Characteristics	Number of patients
Male	44
Female	5
Mean age in years (range)	50 (16–83)
Previous duodenal ulcer	9
Previous perforation	2
NSAIDS	10

NSAIDS, non-steroidal anti-inflammatory medications

Table 2 *Comparison of clinical characteristics of 49 patients with perforated duodenal ulcer in relation to eventual outcome*

	Emergency surgery ($n=7$)	Failed conservative treatment ($n=8$)	Successful conservative treatment ($n=34$)
Mean age (years)	53	49	49
Median duration of perforation (h)	18	5	4
Symptomatic			
Acute (3 months)	3	4	11
Chronic (3 months)	4	4	23
Complications	2	3	3
Median hospital stay (days)	13		8
Mortality	2		1

Failure group

Two patients had sealed perforations at laparotomy: one had been inaccurately assessed and the second had a subphrenic abscess requiring drainage. The nasogastric tube was curled in the oesophagus of another, indicating a failure of management policy.

Four further patients underwent laparotomy after a 12 h trial. All had unsealed perforations and were true failures of conservative treatment. Finally, an 83-year-old woman initially settled but reperforated 4 days later, 12 h after commencement of light diet; laparotomy was performed but death occurred 14 h later of cardiac failure.

Complications

Two patients undergoing immediate surgery died, one of overwhelming sepsis, one of postoperative mesenteric infarction. Two developed postoperative pneumonia.

Six complications occurred in the conservative group: two instances of pneumonia, two of cardiac failure, one prolonged ileus and one subphrenic abscess. One patient (the 83-year-old woman mentioned above) died giving a mortality rate of 2·4 per cent.

Subsequent course

Six successfully treated patients could not be traced. Twenty-eight were followed up for 1–17 years (mean 5·3 years). Twelve (43 per cent) required definitive surgery (median follow-up 5 years). Sixteen did not.

Three died, after at least 4 years follow-up, of unrelated causes. Three had recurrent medically managed ulcers and ten were asymptomatic.

Discussion

Our results using conservative treatment are satisfactory. Thirty-four (81 per cent) were successfully treated. Complications occurred in 14 per cent, and a mortality rate of 2·4 per cent compares favourably with reported surgical mortality. These results were achieved using strict selection of patients and

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regular re-assessment. When conservative treatment failed it was promptly abandoned and operation performed. Nasogastric suction is the vital element in conservative treatment, keeping the stomach empty, allowing sealing of the perforation to take place. Careful positioning of the tube and regular aspiration are important. One patient might not have required laparotomy had an erect chest X-ray been performed showing the tube curled in the oesophagus. The proportion requiring later definitive surgery was similar to that following simple closure[2]. Sixteen patients required no surgery after a median follow-up of 5·3 years. Opposition to conservative treatment relates to the possible consequences of an error in diagnosis. However, as Taylor has shown, with regular re-assessment, problems of misdiagnosis should become rapidly apparent and conservative treatment can then be abandoned. He reported no serious consequences resulting from the short delay in correcting the diagnosis[1]. The chief contra-indications are lack of patient compliance, unsuccessful nasogastric intubation and late presentation. Air swallowing prevents sealing and is suspected if intraperitoneal gas increases despite adequate nasogastric decompression. Using conservative treatment, definitive surgery cannot be performed at the time of perforation, but not all chronic duodenal ulcer perforations require definitive procedures and with the advent of H_2 antagonists the numbers may be even less[3]. Conservative treatment allows time for an accurate ulcer history, for clinical and interval endoscopic assessment and for elective definitive treatment if required.

We do not advocate conservative treatment of all perforated duodenal ulcers but offer it as a reasonable option provided strict criteria and guidelines are followed.

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Artificial pancreas in the diagnosis and treatment of insulinoma: a report of five cases

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The diagnosis of hypoglycaemia in patients with functioning pancreatic islet-cell adenoma or carcinoma presents difficulties[1]. Moreover, surgery can be hazardous in the presence of large fluctuations in blood glucose levels. In addition, multiple tumours are found in some cases[2]. For these reasons the artificial pancreas can be a valuable aid in the management of insulinoma[3,4] and we present five cases where it has been used successfully in both the diagnosis and treatment of organic hypoglycaemia.

Case reports

Case 1

A 52-year-old woman had been investigated for episodes of confusion Fasting blood glucose levels ranged from 40 to 45 mg/dl with insulin levels ranging from 10 to 14 microunits/ml. The patient was connected to an artificial pancreas (AP) (Biostator GCIIS Miles Laboratories). Glucose level fell twice during the night, but was immediately restored by glucose infusion from the AP. Blood samples were withdrawn for assay of insulin and C peptide (IRI, 80 microunits/ml, C peptide, 12 ng/ml). Ultrasonic and radiographic examinations were normal, and no abnormalities were detected on coeliac arteriography Laparotomy was performed with the patient connected to an AP, the rate of dextrose infusion was 200 mg/min. No tumour was found on the first exploration of the pancreas, and infusion rate did not alter greatly. A small tumour was subsequently located at the head of the pancreas, and dextrose infusion rose to 400 mg/min. During tumour removal the dextrose infusion rate was elevated and remained high for 20 min after removal of the tumour; it then fell rapidly and stopped. Histological examination showed an insulinoma. The postoperative course was uneventful.

Case 2

A 67-year-old woman was seen in a state of mental confusion. Plasma glucose was 32 mg/dl. The mental state returned to normal after infusion of glucose. Insulin level was high (62 microunits/ml) as were C peptide levels (9·5 ng/ml). Coeliac arteriography revealed a tumour at the tail of the pancreas. Surgery was performed with the patient connected to an AP. Tumour manipulation was followed by a fall in glucose level with an immediate infusion of 400 mg/min of dextrose from the Biostator to maintain normoglycaemia. After tumour removal, exogenous dextrose was no longer required. Histological examination showed an adenocarcinoma.

Case 3

A 56-year-old man was admitted for incoherent behaviour. Fasting blood glucose concentrations ranged from 35 to 40 mg/dl with insulin levels between 18 and 25 microunits/ml. Abdominal CT scan and arteriographic examinations were normal. Using the AP, euglycaemic hyperinsulinaemic clamp was established. Hyperinsulinaemia failed to suppress endogenous C-peptide secretion, showing autonomous insulin secretion (*Figure 1*). Surgery was performed with the patient connected to an AP. Blood glucose level was kept stable at 85 mg/dl throughout the operation by glucose infusions from the Biostator (150 mg/min). An adenoma was removed and, 17 min after ablation, blood glucose levels returned to normal with no glucose infusion.

Case 4

A 59-year-old man was admitted to hospital for an attack of dizziness. On two occasions blood glucose was 30 mg/dl, although insulin and C-peptide levels were normal. Radiographic examination and coeliac arteriograms were normal. A euglycaemic hyperinsulinaemic clamp gave a positive result (*Figure 1*) The patient was operated upon after being connected to the AP. Blood glucose was kept stable at around 75 mg/dl during the operation with only a low rate of glucose infusion (50 mg/min). An adenoma was removed and 12 min after glycaemia spontaneously rose to 120 mg/dl without any infusion of glucose.

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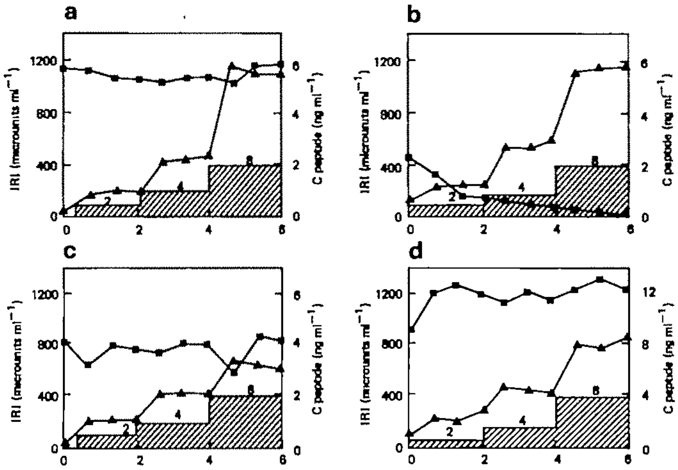

Figure 1 *C-peptide suppression test. Immunoreactive insulin (▲) and C-peptide levels (■) in blood samples from:* **a**, *patient 3,* **b**, *patient 4;* **c**, *controls; and* **d**, *patient 5. The insulin infusion rate* ▨ *during period of attachment to the artificial pancreas is given in microunits kg^{-1} min^{-1}*

Case 5

A 57-year-old man was admitted after a seizure. The physical examination and the EEG were normal. Blood glucose was 45 mg/dl, with insulin and C-peptide levels at 60 microunits/ml and 13 ng/ml respectively Radiographic examination was normal. The euglycaemic clamp demonstrated autonomous secretion of insulin. The patient underwent operation and blood glucose was kept stable at around 78 mg/dl by massive glucose infusions from the AP (350 mg/min). An insulinoma was removed, and 8 min later the blood glucose level stabilized at 95 mg/dl without any glucose infusion.

Discussion

The diagnosis of hypoglycaemia secondary to insulinoma is not straightforward. A low blood glucose level with high insulin and C-peptide levels are strongly suggestive[1], but the secretion of insulin may be paroxysmal[5]. In these cases, glucose monitoring can detect the hypoglycaemic periods as in case 1. A further aid to diagnosis is represented by the C-peptide suppression test[6]. However, the infusion of exogenous insulin exacerbates hypoglycaemia. C-peptide determinations under euglycaemic clamp conditions have demonstrated that infusion of exogenous insulin inhibits endogenous insulin secretion in healthy subjects with, therefore, a fall in C-peptide levels[7]. In contrast, an insulinoma releases both insulin and C peptide autonomously, even in the presence of high concentrations of exogenous insulin (cases 3, 4, 5). This finding points to a diagnosis of insulinoma.

Surgical treatment of a functioning pancreatic islet-cell adenoma is not without difficulties. Although most insulinomas are isolated, it has been estimated that 8–14 per cent are multiple[2]. In these latter cases, persisting infusion of glucose by the artificial pancreas would indicate incomplete tumour removal. Karam has reported a case in which the persistent infusion of dextrose enabled detection of two other microadenomas[3]. Other workers have also noted that a rise in the blood glucose level during surgery for an islet-cell insulin-secreting tumour is a good indicator of complete removal of the insulinoma[8]. An increase in blood glucose or a fall in the infusion of dextrose by the AP within 15 and 30 min after the resection has often been considered as an indicator of the complete removal of the tumour; this was observed in all our cases. Anaesthetic management can be difficult during operation of such tumours, and is often made rather hazardous by the wide swings in blood glucose levels in the absence of continuous glycaemic monitoring: a dangerous and undetected hypoglycaemia may occur before removal of the tumour. Continuous administration of glucose may also increase postablational hyperglycaemia. Blood glucose concentration therefore needs to be determined frequently so that glucose can be administered only when the glucose level falls. The artificial pancreas is of particular value in the control of glood glucose during the operative period in such patients. It can be seen to be of help in both the diagnosis and the surgical treatment of insulinomas.

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Short notes

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Comparison of polyglactin 910 and nylon in skin closure

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Cosmetic and comfort advantages have been claimed for subcuticular skin closure. Increased convenience and cost benefits of avoiding suture removal with an absorbable suture have also been reported[1–3]. However, it seems to be widely believed that subcuticular polyglactin leads to excess tissue reaction and subsequent 'keloid-like' hypertrophy[4]. The study reported here was therefore designed to compare cosmetic results, complications and patient preference between subcuticular polyglactin and standard sutures of nylon.

Patients and methods

Seventy-seven patients undergoing varicose vein surgery had alternate incisions on the same leg closed with either Vicryl (polyglactin 910; 159 incisions) or Ethilon (nylon, 166 incisions). At 10-day review, sutures were removed and wounds later were inspected by surgical registrars involved in the study. Wounds were inspected without documentary evidence of type of closure. Any evidence of bruising, stretching, pigmentation or hypertrophy of the scars was recorded. The incisions were again inspected 6 weeks and 6 months after surgery, and the patients were questioned about complications, antibiotic usage and whether they had any preference for either suture technique.

Results

All patients were reviewed at 10 days and at 6 weeks, but one patient was lost to follow-up thereafter. No difference in induration or bruising was seen between wounds closed with polyglactin or nylon. No patient had used antibiotics for wound problems. Hypertrophic scarring was equally uncommon with polyglactin and nylon (*Table 1*). One 'keloid' scar was seen with interrupted nylon. At 6 weeks, 16 Vicryl (10 per cent) and 15 Ethilon (9 per cent) scars were noted to be pigmented, but the numbers of such pigmented scars in both groups had halved at the end of the review period. At 6 weeks 11 (7 per cent) scars in the nylon group and 7 (4 per cent) in the polyglactin group were unduly stretched; whereas 6 (4 per cent) wounds closed with polyglactin were still wide at 6 months, 15 scars (10 per cent) in the nylon group had stretched.

By 6 months, most scars had faded, although 56 (35 per cent) incisions closed with nylon still showed 'unsightly' marks, and 2 (1 per cent) were severely cross-hatched.

One-half of patients at all clinic visits stated that they preferred subcuticular closure; less than 10 per cent preferred interrupted nylon sutures.

Table 1 *Assessment at 6 months of skin closure with polyglactin or nylon*

	Polyglactin		Nylon	
Complications	Incisions	Percentage	Incisions	Percentage
Hypertrophic scarring	5	3·2	7	4·3
Keloid scarring	—	—	1	0·6
Pigmented scars	8	5·1	7	4·3
Mild stretched scars	5	3·2	14	8·6
Badly stretched scars	1	0·6	1	0·6
'Unsightly' suture marks	—	—	56	34·4
'Ugly' suture marks	—	—	2	1·2
Preference	Polyglactin 39 (51·3%)		Nylon 7 (9·2%)	

Discussion

There was no difference in the incidence of hypertrophic or pigmented scars, although a stretched scar was more common with interrupted sutures. Stretching of scars grew worse between 6 weeks and 6 months with nylon sutures, but not with subcuticular polyglactin. This suggests that the long-term support of the wound provided by polyglactin is responsible for better results. Cross-hatched scars are the most unsightly result of wound closure with interrupted nylon. Suture marks were usually so obvious even at the 6-month review that a 'blind' appraisal of the scar was not possible.

Subcuticular suturing theoretically should be the ideal skin closure. Polyglactin 910 (Vicryl) may be the best suture for subcuticular use: it handles well, is flexible, very strong and absorption is nearly complete by 70 days. In contrast, 50 per cent of a polyglycolic acid (PGA – Dexon) suture remains at 90 days, and considerable amounts are still present at 120 days[5]. Theoretically, therefore, any adverse reaction from polyglactin should be less than that from PGA as its persistence in the tissues is much less. The material, length for length, is about twice the price of nylon, but in subcuticular use a shorter suture is used and the costs may be less. Suture removal is not required, and district nurses and clinics are freed for more important duties. Our study has failed to demonstrate any disadvantages and has shown many advantages from the use of subcuticular polyglactin. The clear message from the patients was that they preferred polyglactin subcuticular closure to interrupted nylon sutures.

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Surgical Research Society

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The 67th Meeting of the Surgical Research Society took place on 7 and 8 January 1988 at the University of Ulster, Jordanstown. The Meeting was organized by the Department of Surgery, The Queen's University of Belfast, and Professor G. R. Giles was in the Chair. A Symposium entitled 'Management of extrahepatic biliary obstruction' preceded the free paper sessions. Ninety-five papers were read, and the Patey Prize was awarded to Mr R. Miller for his presentation entitled 'Ambulatory anorectal manometry: a new technique for the investigation of anorectal function'. A selection of papers and abstracts is published on pp. 587–618.

Bile acid concentrations in the refluxate of patients with reflux oesophagitis

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Although reflux of bile acids has been implicated in the pathogenesis of reflux oesophagitis, attempts to document this in vivo *have failed to detect more than trace amounts of bile acid in the oesophagus. To determine the bile acid composition of oesophageal refluxate, 45 patients with abnormal acid gastro-oesophageal reflux with oesophagitis and 10 controls had a size 14 Fr Salem sump tube positioned 5 cm above the lower oesophageal sphincter. Oesophageal contents were continuously aspirated and collected in aliquots every 2 h over 16 h. Fasting, postprandial, upright and supine (nocturnal) periods were assessed and total conjugated bile acids were measured by high pressure liquid chromatography with a sensitivity of 8 μmol/l. Conjugated bile acids were detected in 2 of 10 controls (maximum 40 μmol/l) and in 39 of 45 patients (87 per cent). Eleven patients had peak conjugated bile acid levels >200 μmol/l, and these levels occurred exclusively during the supine (nocturnal) period. Median conjugated bile acid levels during daytime reflux were <20 μmol/l which was significantly lower than during nocturnal reflux (median 51 μmol/l, $P<0.001$). Conjugated bile acids are detected in the oesophagus of most patients with oesophagitis and may play a role in the pathogenesis of oesophagitis in some patients with nocturnal gastro-oesophageal reflux.*

Keywords: Gastro-oesophageal reflux, bile acids

In 1935 Asher Winkelstein[1], a New York physician, proposed that oesophagitis was caused by the reflux of gastric juice into the oesophagus. This was formally documented 20 years later[2], and the presence of acid and pepsin in the oesophagus is now well established in the pathogenesis of this condition. Many patients, however, were not helped by antacids or, more recently, by H_2 antagonists and it has been suggested that reflux of bile acids and duodenal contents may also have a role to play[3–6]. Bile contaminated gastric juice has been found in the stomachs of patients with gastro-oesophageal reflux[7–9], but attempts to recover bile acids from the oesophagus of these patients have shown only trace amounts[10,11]. Investigations to date have concentrated on the daytime period, while many patients complain of heartburn during the night. In order to investigate the possibility of supine bile acid reflux we undertook a prolonged (16 h) aspiration study to include the entire nocturnal period.

Patients and methods

Patients

Forty-five patients with chronic gastro-oesophageal reflux (symptoms for >6 months) were entered into the study after giving informed consent. There were 31 men and 14 women with a median age of 56 years (range 24–85 years). Before entry, gastro-oesophageal reflux was confirmed in all patients on the basis of abnormal endoscopy (Savary–Miller Grades II–IV) and a positive De Meester score on 24 h ambulatory out-patient pH monitoring (median percentage time that pH <4 = 11·4 per cent, range 4·5–35·6) Two patients had had failed antireflux surgery elsewhere but no patient had undergone any form of gastric resection or pyloroplasty.

For comparison, ten asymptomatic volunteers (six men, four women; median age 58 years, range 32–78 years) underwent an identical study to determine the bile acid content of physiological reflux episodes. All control subjects had a normal score on 24 h ambulatory pH monitoring, but they did not undergo endoscopy

Methods

Patients and control subjects were fasted for 6 h and all medications likely to influence gut motility or secretion were withheld for 48 h before commencement of the investigation. A size 14 Fr Salem sump tube with attached antimony pH electrode (Synectics Medical, UK) was positioned with its tip 5 cm above the manometrically located lower oesophageal sphincter. Used in the conventional way, this tube behaves as an 'air vented' tube rather than as a true sump tube and within the oesophagus it is frequently occluded by mucus. Suction applied to the air vent converts the tube into a true sump tube with infrequent blockages, minimal mucosal trauma and a high efficiency at high rates

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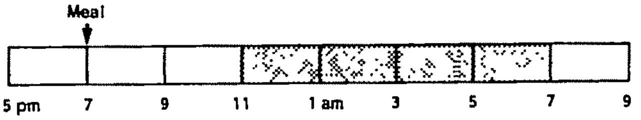

Figure 1 *Diagram of the aspiration study showing the time periods examined* ☐, *Upright*, ▨, *supine*, ↓ *indicates the time of a meal*

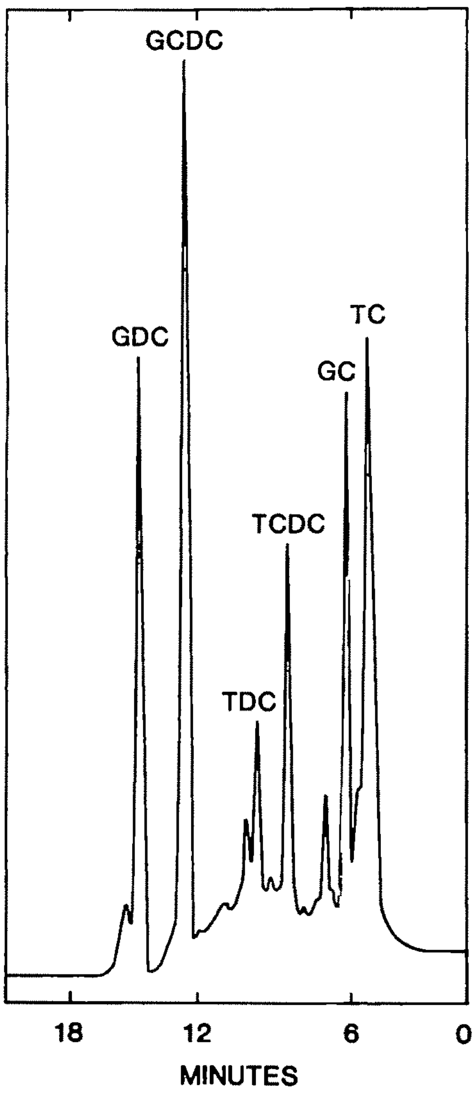

Figure 2 *Chromatogram of a specimen of oesophageal aspirate showing the six bile acid peaks. GDC, glycodeoxycholate, GCDC, glycochenodeoxycholate, TCDC, taurochenodeoxycholate, TDC, taurodeoxycholate, GC, glycocholate, TC, taurocholate*

of air flow. The tube–electrode assembly was inserted transnasally at least 1 h before the study in order to minimize intubation effects on oesophagogastric motility, continuous aspiration was maintained for 16 h with aliquots being collected every 2 h Study design allowed fasting, postprandial, upright and supine periods to be assessed (*Figure 1*). Subjects sat in a chair during the upright period of the study and retired at 23.00 hours to be woken at 07.00 hours. Patients were able to sleep with their usual number of pillows, and refrained from taking medications of any kind during the investigation.

Specimens were collected on ice, separated from mucus by a fine wire mesh, centrifuged at 7000 r.p.m for 20 min and stored at −70°C for later analysis. Continuous pH monitoring was maintained with a solid state digital recorder (Synectics Medical) and the data were processed by microcomputer (Amstrad PC 1512HD20). The pH electrodes were calibrated in buffers of pH 7·01 and 1·07 before and after each study.

Bile acid analysis. Bile acid amidates were assayed for by high performance liquid chromatography using a modification of the technique of reversed phase, ion paired/ion suppression chromatography[12,13], developed and validated for use with gastric samples in our department. Briefly, we have used an acidified mobile phase (pH 2·5) of acetonitrile in water (54 per cent), with tetrabutylammonium phosphate added as the counter ion. Two columns in series (Ultrasphere ODS 5 μm, Altex Scientific, USA; Micropak C18, Varian, USA) were employed to enhance the separation of cholate amidates The elution profile of the six most common bile acid conjugates is completed within 18 min (*Figure 2*). Sensitivity for pure bile acid standards in gastric juice is 8 μmol for detection, however, quantification is not reliable below 20 μmol and on assayed samples these values are referred to as 'trace'. The assay is linear for all bile acid conjugates from 20 μmol to 10 mmol/l Bile acids were extracted with methanol (1:2), centrifuged and filtered through a 0·22 μm Millex filter (Millipore, Molsheim, France) and injected into the chromatograph (Gilson model 302). Statistical analyses were performed using the Mann–Whitney U test.

Results

Oesophageal aspirate was obtained during 328 of 360 patient time periods, and from 46 of 80 control subject time periods. Bile acid conjugates were detected in the aspirate from two of ten asymptomatic subjects on a total of six occasions; all levels were trace amounts except one postprandial specimen with a concentration of 40 μmol/l. These time periods all corresponded to periods during which asymptomatic acid reflux was demonstrated by pH monitoring.

Of 45 patients, 39 (87 per cent) demonstrated at least trace amounts of bile acid during at least 1 collection period over the 16 h of the study, with a tendency toward a higher prevalence of bile acid contaminated oesophageal refluxate during the supine period (*Figure 3*). Overall detectable bile acids were present in 211 of 360 time periods (59 per cent) and were quantifiable (>20 μmol/l) in 57 (16 per cent). Median levels for the fasting, postprandial and upright periods, however, were low and there was no significant difference in bile acid levels between these periods (*Table 1*). In contrast, higher conjugated bile acid levels were observed during the supine (nocturnal) period with a median level of 51 μmol/l and range of 0–15 283 μmol/l ($P < 0{\cdot}001$ *versus* fasting, postprandial or upright).

Of the 45 patients, 11 demonstrated peak conjugated bile acid levels in excess of 200 μmol/l and these levels were found exclusively during the supine period (*Figure 4*). Episodes of acid gastro-oesophageal reflux were recorded in all time periods during which conjugated bile acids were detected, except for one patient who demonstrated high conjugated bile acid levels during the nocturnal period (peak conjugated bile acid level,

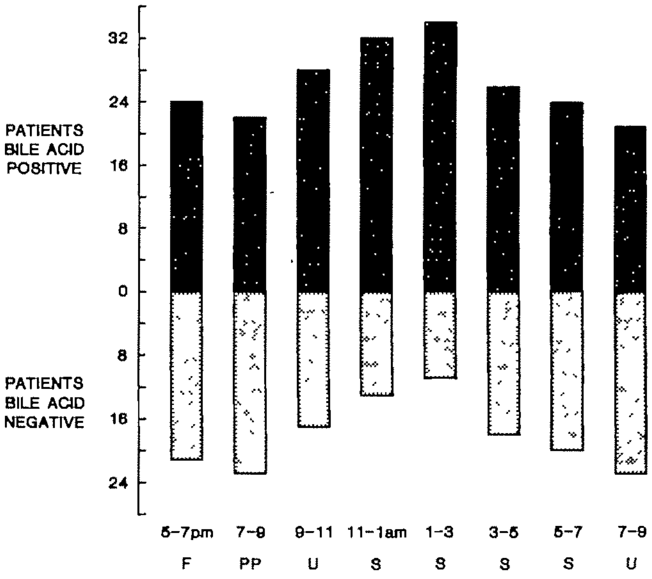

Figure 3 *Bar chart of the number of patients with and without bile in their oesophageal aspirate for each of the eight time periods studied. F, fasting, PP, postprandial, U, upright, S, supine*

Table 1 *Bile acid levels*

Study periods	Median (μmol/l)	Range (μmol/l)
Fasting	<20	0–187
Postprandial	<20	0–94
Upright	<20	0–105
Supine	51	0–15 283*

* $P<0{\cdot}001$, supine *versus* all other periods

15 283 μmol/l) and no acid reflux. This patient had alkaline intra-oesophageal drift (to pH 8·0) during the night but demonstrated typical acid reflux episodes during the daytime period.

Discussion

This study has clearly shown that bile acids do reflux into the oesophagus of symptomatic patients and that most of this reflux occurs during supine rest. The damaging effects of duodenal contents on the oesophagus have been documented following total gastrectomy and oesophagojejunostomy[4,15]. Oesophagitis has been observed in achlorhydric patients with pernicious anaemia[4,16], suggesting that duodenal contents may contribute to oesophagitis in patients with intact stomachs. Conjugated bile acids in an acid medium have been shown to disrupt the oesophageal mucosal barrier and cause cytotoxic damage to mucosal cells[17–19], but are not damaging at a neutral pH[6,20]. The presence of conjugated bile acids in refluxate during acid reflux episodes has the potential, therefore, to contribute to the pathogenesis of oesophagitis.

Whilst early intubation studies in patients with hiatus hernia and oesophagitis suggested increased duodenogastric reflux in these patients compared with controls[7,8,21], more recent studies have disputed these findings[9,22–26]. Aspiration studies, however, have shown that bile acids are frequently found in the gastric juice of patients with reflux oesophagitis, and are therefore potentially available for reflux into the oesophagus. Aspiration of gastric contents from the most dependent part of the stomach may provide unreliable information about the concentration of bile acids in gastric juice bathing the lower oesophagus during reflux, as there is a decreasing gradient of bile acid concentration from the antrum to the cardia[21]. This has prompted studies utilizing direct oesophageal aspiration and analysis, and these have failed to detect more than small amounts of bile acid in the oesophagus[10,11]. However, these studies have only assessed daytime reflux, and our results for this period are in broad agreement with those of Smith *et al.*[10]. Our study represents the first analytical study of nocturnal bile reflux. The high bile acid concentrations found in some patients during sleep may be due to several factors. Decreased gastric secretion during the night[27] may reduce dilution of refluxed duodenal secretions, and the cessation of salivation which occurs during sleep[28] may result in less dilution of collected oesophageal refluxate. Increased nocturnal duodenogastric reflux, however, probably accounts for the peak levels seen in some of our patients. Bile contaminated gastric juice has been more commonly found at night in patients with peptic ulcer and controls[27,29,30], and gastric bile acids are found in higher concentration than during the daytime[27]. In this study, when high bile acid levels were recorded in the oesophagus, the phenomenon was transient and occurred in usually only one or, at most, two collection periods. This is consistent with the findings of Gotthard and colleagues, who noted broad fluctuations in gastric bile acid levels from hour to hour during the night in their patients[27].

There is no current non-invasive technique available to quantify bile acids in the oesophagus accurately. Naso-oesophageal intubation was therefore required in this study and has undoubtedly influenced results. Nasopharyngeal intubation increases basal salivary flow up to threefold[31] and increases the rate of swallowing[32]; this has the tendency to dilute collected oesophageal secretions and therefore understate bile acid concentrations in refluxate, particularly during the awake period. The median duration of nocturnal reflux episodes was 5·5 min and, since each sample represents collected oesophageal secretion, saliva and refluxate over a 2 h period, bile acid concentrations are likely to be higher during actual reflux episodes. Mittal used a dental aspirator to exclude saliva, but this was found to be impractical for a study of 16 h duration[11]. In order to minimize motility disturbances induced by intubation itself, the sump tube was positioned at least 1 h before commencement of the study. The effects of the tube on oesophageal motility and gastro-oesophageal reflux are largely unknown. However, a comparison between ambulatory pH monitoring in each patient before and during the study showed no significant difference in acid exposure or clearance.

Previous studies of gastric and oesophageal bile acid levels have used the 3α-hydroxysteroid dehydrogenase enzymatic technique of analysis[33]. A recent report of cross reactivity between the dehydrogenase enzyme and 3α-hydroxyl groups present in other sterols besides bile acids, highlights the non-specific nature of this assay and its unreliability when used with postprandial gastric samples[11]. High performance liquid chromatography is a sensitive and specific assay technique and is currently the assay of choice for conjugated bile acids. It has the additional advantage of providing a profile of individual bile acid amidates. We assayed for the six most prevalent bile acid conjugates which make up 98 per cent of hepatic bile acids[34,35] We found no unconjugated bile acids in any samples by thin layer chromatography. Free bile acids in the upper gastro-intestinal tract result from bacterial deconjugation of bile acid amidates[36] and are only found in minute amounts in a small proportion of subjects with intact stomachs[30]. Continuous intra-oesophageal pH monitoring during the study revealed acid reflux episodes during the majority of time periods when bile acids were detected in the oesophagus. This study indicates that bile acids frequently reflux into the oesophagus during acid reflux episodes, detected during routine prolonged pH monitoring, and warrants a note of caution in the interpretation of 'alkaline' gastro-oesophageal reflux within the oesophagus as reflux of duodenal contents. Gastric juice containing potentially cytotoxic levels of bile acid frequently has a pH of < 3·5, a pH which would be registered as an acid reflux event in the oesophagus[9].

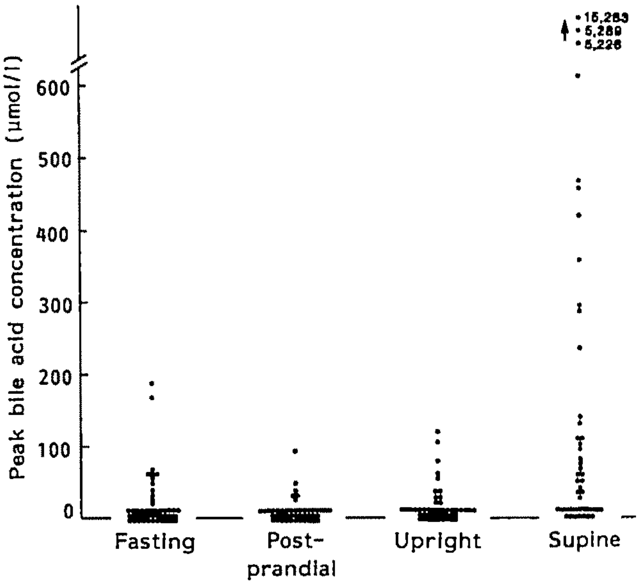

Figure 4 *Peak bile acid concentration (μmol/l) for each patient during the four different situations assessed Supine is the highest of four and upright highest of two periods per patient*

The cytotoxic potential upon the oesophagus of levels of conjugated bile acids found in this study is difficult to determine. Whilst levels of >1 mmol/l have caused mucosal barrier disruption *in vivo*[17,18,20,37], the effects of lower concentrations of the order found in the majority of the patients in this study have not been extensively investigated. Hopwood *et al.*[38] have found ultrastructural damage in human oesophageal mucosal epithelium after 5 min incubation in 200 μM bile acid solution at an acid pH. Furthermore, reflux of HCl and bile acid is unlikely to occur in the absence of pepsin *in vivo* and, as bile acid and pepsin appear to have different sites of action on oesophageal epithelium[39], their effects may be additive. The effects of bile acids on a mucosa already denuded by acid and pepsin are unknown.

This study has shown that patients with acid gastro-oesophageal reflux and oesophagitis frequently have conjugated bile acids, detectable at some time during the day, in their oesophageal refluxate. In most cases, however, levels are minute and of doubtful clinical significance. Some patients, in our series 24 per cent, have potentially cytotoxic levels of >200 μmol/l, and these levels only occurred during the noctural (supine) period. Bile acids may therefore be important in the pathogenesis of oesophagitis in some patients with nocturnal gastro-oesophageal reflux.

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Augmentation of lymphokine-activated killer cell activity in patients with gastrointestinal cancer

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Adoptive cellular immunotherapy with lymphokine-(interleukin 2) activated killer (LAK) cells is not as successful in patients with gastrointestinal cancer as with other tumour types. This may be because the cytotoxic capacity of LAK cells from such patients is suboptimal. In this study we have sought to augment this activity by stimulating the lymphocytes with recombinant human interferon-γ (r-HuIFN-γ) in addition to interleukin 2 or by depleting the lymphocytes of adherent suppressive mononuclear cells. Both procedures augment LAK activity in gastrointestinal cancer patients but adherent cell depletion results in fewer cells being available for adoptive cellular immunotherapy. No further augmentation of LAK activity of adherent cell depleted cells could be accomplished by addition of r-HuIFN-γ. Co-stimulation of unfractionated peripheral lymphocytes with r-HuIFN-γ is the preferable procedure for the generation of LAK cells for adoptive cellular immunotherapy in patients suffering from gastrointestinal cancer.

Keywords: Adoptive cellular immunotherapy, lymphokine-activated killer cells, interleukin 2, interferon-γ, adherent cells

The concept of adoptive cellular immunotherapy for patients suffering from advanced malignant disease[1] has taken a step forward with the recent reports from the section of surgery in the National Institutes of Health on the use of *in vitro* stimulated lymphokine-activated killer (LAK) cells and recombinant interleukin 2[2,3]. The principles underlying this approach involve the activation of the patient's own lymphocytes *in vitro* with high concentrations of interleukin 2 for several days during which time they become highly cytotoxic towards tumour, but not normal[4], cells and may then be re-infused together with further interleukin 2 in order to maintain their cytotoxic capacities *in vivo*. This procedure is almost universally successful in treating experimental animal tumours when the LAK cells are obtained from normal, non-tumour bearing syngeneic animals[5–9]. However, despite some dramatic successes claimed by two independent centres[3,10] in the USA with this approach, it is evident that of the 200 patients treated so far, therapeutic failure occurs in 60–70 per cent of patients including many patients with gastrointestinal cancer.

We have recently demonstrated that LAK cell generation is impaired in patients suffering from advanced gastrointestinal cancer[11]. We therefore postulated that one possible cause of therapeutic failure in such patients was that the autologous cytotoxic lymphocytes re-infused into patients with advanced disease were not expressing their maximal antitumour lymphocytotoxicity. It is evident that, in order to maximize this therapeutic potential, means are required of augmenting this cytotoxicity.

LAK cells are derived from a subset of peripheral blood mononuclear cells known as natural killer cells[12], so called because they can spontaneously kill several cultured cell lines but not solid autologous tumours. However, their transformation into LAK cells under the influence of interleukin 2 does cause them to become cytotoxic against autologous tumour cells. *In vivo* natural killer cells are derived from lymphoid precursor cells and the maturation process is under the influence of a number of regulatory factors such as interferons[13], known to be stimulatory to this differentiation pathway, and monocytic cells[14] which have an inhibitory effect on the development of mature natural killer cells. If these two regulatory influences have similar effects in regulating LAK cell development from natural killer cells then manipulating their actions may be one way of boosting the cytotoxicity of LAK cells for therapeutic purposes.

In this study we have attempted to augment LAK cytotoxicity in patients with gastrointestinal cancer both by removal of adherent monocytic cells and by co-stimulating lymphocytes with recombinant human interferon-γ (r-HuIFN-γ) in addition to interleukin 2 during LAK cell generation.

Patients and methods

Natural killer and LAK cell activity before and after adherent cell depletion, and with and without r-HuIFN-γ co-stimulation has been measured in a total of 19 age-matched control subjects and 31 patients with gastrointestinal cancer. Patients in the control group were patients admitted for elective surgery for non-malignant conditions (e.g. herniorrhaphy, cholecystectomy) or who were being investigated for non-malignant disease.

The gastrointestinal cancer group consisted of 5 patients with primary gastric cancer and 26 with colorectal cancer Tumours were regarded as being advanced if there was clinical, radiological or subsequent histopathological evidence of extra-serosal tumour spread Using these criteria 27 of the 31 patients had advanced disease and all studies were performed before surgery for the primary tumour and without knowledge of the tumour stage at the time

No patients in either group were receiving treatment with drugs known to have immunomodulatory properties (e.g. steroids, H_2-receptor antagonists) and none had previously received allogeneic blood transfusions

Immunological studies

A total of 40 ml of venous blood was drawn from each subject at the same time each morning and collected in tubes containing five drops of preservative free heparin.

Peripheral blood mononuclear cells were isolated from these samples on Ficoll Hypaque density gradients (Sigma Chemicals Company Ltd, UK) and resuspended in RPMI 1640 medium containing glutamine (Gibco Ltd.) with 10 per cent fetal calf serum (Gibco Ltd.), amphotericin B 2.5 μg/l (Gibco Ltd.), gentamicin

160 μg/l, sodium pyruvate 2 μmol/ml and non-essential amino acids—hereinafter referred to as complete medium. After washing twice in Hank's balanced salt solution the cells were corrected to a cell density of 5×10^6 viable cells/ml. The natural killer activity of these cells was measured as described below and the remaining cell suspension was divided into two aliquots. Adherent cells were removed from one aliquot, whereas the remaining aliquot remained unfractionated.

To deplete adherent cells, peripheral blood mononuclear cells at a cell density of 5×10^6 cells/ml were diluted with an equal volume of fetal calf serum deficient complete medium. This cell suspension was then placed in 10 cm diameter plastic petri dishes (Nunc, Denmark) so that the cells just coated the bottom of the plate. The plates were then incubated for 1 h at 37°C in a humidified atmosphere of 5 per cent CO_2 in air and non-adherent cells were gently washed from the plate with chilled (4°C) Hank's balanced salt solution.

Cells were spun down and resuspended in complete medium before being counted and corrected to a concentration of 5×10^6 cells/ml. The natural killer cell activity of this aliquot was measured and the remaining lymphocytes used for LAK cell generation with and without r-HuIFN-γ. This procedure was effective in removing monocytic cells as measured by immunofluorescence with the OKM1 monoclonal antibody.

The percentage recovery of cells after adherent cell depletion was calculated from the knowledge of the numbers of cells used for adherent cell depletion and the numbers recovered after this procedure.

LAK cell generation

Two aliquots of 15×10^6 cells, either unfractionated or adherent cell depleted, were each suspended in 10 ml of complete medium in separate 50 ml tissue culture flasks (Nunc, Denmark). Human purified interleukin 2 (highly purified lectin-free interleukin 2, Biotest Pharma, GmbH) was added to each flask to a final concentration of 500 units/ml. To one of the two flasks r-HuIFN-γ (kindly provided by Dr Kellerman, Roche, Basle) was added to a final concentration of 200 units/ml. The concentrations of the two agents were chosen to provide maximal LAK cell generation in preliminary dose–response studies (data not shown). The flasks were placed upright in incubators at 37°C in humidified air containing 5 per cent CO_2 and left undisturbed for 3 days.

After this 3-day incubation period, cells were harvested, counted and corrected to 5×10^6 cells/ml in complete medium and their cytotoxicity measured in the chromium-51-release assay.

Cytotoxicity assays

As previously described[15], the erythroleukaemia cell line K562 was employed as the target cell for assessment of natural killer cell activity in adherent cell depleted and non-depleted peripheral blood mononuclear cell populations.

LAK cell cytotoxicity was assessed both against the lymphoblastoid target DAUDI which is the international reference target for LAK cell activity and the colorectal adenocarcinoma cell line COLO 320. Both of these latter cell lines are resistant to natural killer activity.

In each case target cells were labelled with 100 μCi sodium [^{51}Cr] chromate (Radiochemical Centre, Amersham, UK) according to methods previously described by us[15], and corrected to a final concentration of 1×10^5 cells/ml in complete medium. Effector cells (fresh lymphocytes for the natural killer cell activity assay and interleukin 2 activated lymphocytes for the LAK cytotoxicity assay) at a concentration of 5×10^6 cells/ml were distributed in 100 μl aliquots in serial doubling dilutions into round bottomed microtitre plates (Nunc, Denmark). To each 100 μl aliquot of effector cells 100 μl of the appropriate target cell was added such that effector:target ratios of 50:1 down to 6·25:1 were achieved. All such measurements were performed in triplicate. The plates were incubated in humidified air containing 5 per cent CO_2 at 37°C for exactly 4 h after which 100 μl of the supernatant was collected from each well and counted for radioactivity in a Philips Gamma Counter.

The spontaneous and maximal specific ^{51}Cr release was determined by incubating 10^4 target cells with complete medium and detergent respectively. The percentage of specific ^{51}Cr release at each effector target cell ratio was calculated from the formula:

$$\frac{\text{mean experimental } ^{51}\text{Cr release} - \text{spontaneous } ^{51}\text{Cr release}}{\text{maximal } ^{51}\text{Cr} - \text{spontaneous } ^{51}\text{Cr release}} \times 100$$

Owing to the large numbers of lymphocytes required to perform all the above tests, it was not possible to perform all paired tests on all patients and the total numbers of patients on whom each paired component of the study was performed is indicated at the foot of each diagram.

Statistical analysis

Statistical analyses were performed on all data using the paired *t* test. A probability value of <0·05 was regarded as being statistically significant. The data presented are expressed as mean ± s.e.m.

Results

All results are expressed as the mean ± s.e.m. percentage cytotoxicity at an effector:target cell ratio of 50:1. Identical effects were seen at the lower effector:target cell ratios.

Natural killer cell activity (Figure 1)

Natural killing of the K562 cell line by fresh unseparated peripheral blood mononuclear cells was similar in both control subjects and patients with gastrointestinal cancer. Removal of adherent cells in both groups resulted in statistically significant augmentation of natural killer cell activity (from 21·5 ± 3·8 to 38·6 ± 5·2 per cent, P<0·001 in control subjects and from 21·7 ± 1·7 to 34·3 ± 3·2 per cent, P<0·001 in patients with gastrointestinal cancer). However, a substantial loss of lymphocyte numbers was incurred in both groups during the adherent cell depletion procedure (35·6 ± 9·8 per cent for control subjects and 41·0 ± 2·6 per cent in the cancer group).

LAK cell activity before and after adherent cell depletion

As can be seen in *Figures 2* and *3*, LAK cell activity in patients with gastrointestinal cancer was significantly lower than that of controls (P<0·05 and P<0·02 respectively).

The LAK cell cytotoxicities of both unfractionated and adherent cell depleted lymphocytes after 3 days incubation in interleukin 2 are summarized in *Figure 2*. Removal of adherent cells resulted in significant elevation of LAK cell cytotoxicity in gastrointestinal cancer patients against both targets (from 20·4 ± 4·1 to 35·0 ± 3·5 per cent, P<0·001 against DAUDI and from 14·9 ± 3·5 to 20·9 ± 4·0 per cent, P<0·02 against COLO 320).

A significant rise in cytotoxicity against the DAUDI target (from 24·5 ± 3·4 to 30·2 ± 4·0 per cent, P<0·05) was noted after adherent cell depletion in control subjects, and although the trend was similar against the COLO 320 target (from 27·3 ± 7·4 to 32·2 ± 6·8 per cent) this did not reach statistical significance.

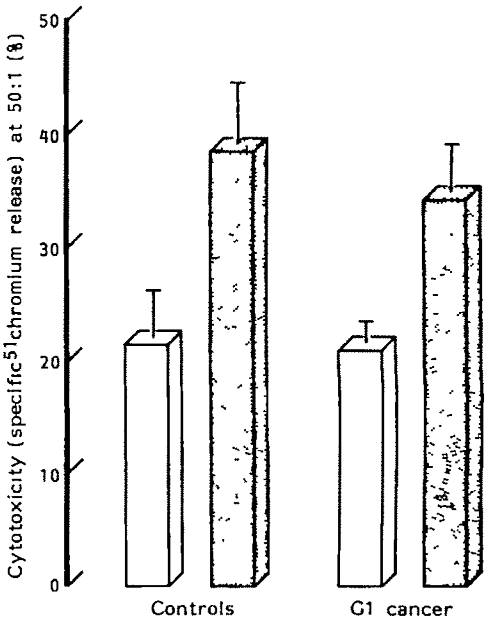

Figure 1 *Natural killer cell activity before (□) and after (▨) adherent cell depletion in controls (mean cell loss 35·6 ± 9·8 per cent, P<0·001) and gastrointestinal cancer patients (mean cell loss 41 ± 2·6 per cent, P<0·001)*

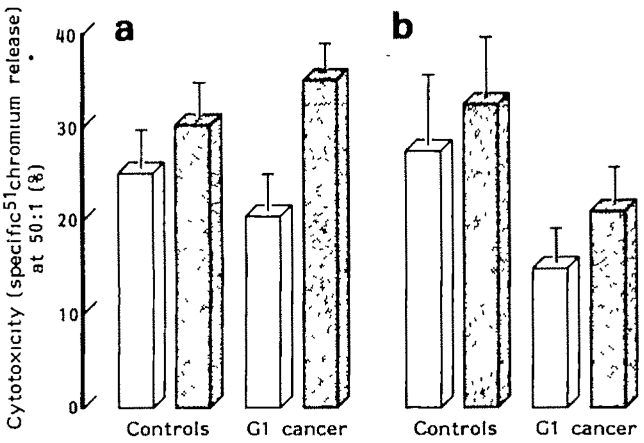

Figure 2 *LAK cell activity before (□) and after (▨) adherent cell depletion in controls and gastrointestinal cancer patients against* **a** *the DAUDI tumour target (controls* n = *15,* P<*0·05, cancer patients* n = *16,* P<*0·001);* **b** *the COLO 320 tumour target (controls* n = *10, n.s., cancer patients* n = *16,* P<*0·02)*

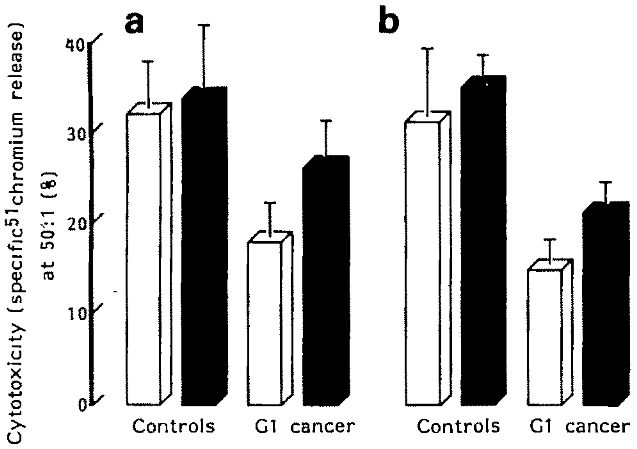

Figure 3 *LAK cell activity of unseparated mononuclear cells with (■) and without (□) r-HuIFN-γ in controls and gastrointestinal cancer patients against* **a** *the DAUDI tumour target (controls* n = *10, n.s.; cancer patients* n = *15,* P<*0·03),* **b** *the COLO 320 tumour target (controls* n = *8, n.s., cancer patients* n = *6, n.s.)*

LAK cell activity in unfractionated peripheral blood mononuclear cells with and without r-HuIFN-γ

Figure 3 summarizes the results of co-stimulation of unfractionated peripheral blood mononuclear cells with 200 units/ml r-HuIFN-γ in addition to interleukin 2 for control subjects and gastrointestinal cancer patients. Co-stimulation of these peripheral blood mononuclear cells with r-HuIFN-γ resulted in statistically significant augmentation of LAK cell activity in lymphocytes from cancer patients (from 18·0 ± 4·0 to 26·3 ± 4·5 per cent, $P < 0.03$) against the target DAUDI at a 50 1 effector:target ratio. A similar trend was seen when these cells were tested against the COLO 320 target (from 15·0 ± 2·8 to 21·0 ± 2.7 per cent) but this difference failed to reach statistical significance.

A slight but statistically insignificant increase in LAK cytotoxicity of control subjects was observed after co-stimulation with r-HuIFN-γ (from 32·0 ± 5·1 to 33·8 ± 8·0 per cent against DAUDI and from 31·4 ± 8·4 to 35·5 ± 8·9 per cent against COLO 320).

Combination treatment of lymphocytes by adherent cell depletion and r-HuIFN-γ co-stimulation

As can be seen in *Figure 4* the LAK activity of adherent cell depleted lymphocytes, whether from control subjects or gastrointestinal cancer patients, was not further augmented by co-culture with r-HuIFN-γ, irrespective of the target cell employed.

Discussion

The contribution of immunobiotechnology to cancer therapy is now leaving the realm of the theoretical and entering clinical application[16]. Of these approaches the use of adoptive cellular immunotherapy with *in vitro* activated lymphocytes, whose cytotoxic function is directed against tumour cells but not normal cells, is currently the subject of enormous interest However, the almost universal success of this treatment with LAK cells in experimental animals has not translated quite so successfully into clinical practice, particularly in patients suffering from gastrointestinal cancer[2,10]. Our efforts have been directed to determining why this should be the case when cytotoxic lymphocytes capable of killing gastrointestinal cancer cells *in vitro* can be readily elicited from the lymphocytes of healthy humans[17] and animals[18]. We have previously reported that the generation of LAK cells in patients suffering from advanced gastrointestinal malignancy is impaired in comparison with that of healthy subjects and patients suffering from localized disease[11]. This is perhaps not surprising in view of the general suppression of lymphocyte responsiveness which accompanies progressive gastrointestinal cancer[19]. Accordingly, if adoptive cellular immunotherapy of this type is to have any hope of success in these patients it seems logical to try to identify means of augmenting this antitumour lymphocytotoxicity. The present study was designed with this aim in view, based on the knowledge that the maturation of the LAK cell precursor is influenced by interferons which exert a stimulatory effect on this maturation process and adherent monocytic cells which in general inhibit the maturation. Our hypothesis was, therefore, that removal of adherent cells or co-stimulation of the lymphocytes with genetically engineered r-HuIFN-γ would augment the impaired cytotoxicity of lymphocytes from gastrointestinal cancer patients on incubation for several days in the presence of interleukin 2.

As can be seen in *Figures 1* and *2*, removal of adherent cell from the peripheral blood lymphocyte populations of both controls and gastrointestinal cancer patients significantly augmented both the natural killer cell LAK precursor and LAK cell cytotoxicity against the natural killer resistant tumour target cells. However, this has the unfortunate effect of resulting in the loss of some 30–40 per cent of the initial lymphocyte population thus reducing the numbers of cells available for re-infusion for therapeutic purposes. This is important because it has been demonstrated that the therapeutic effect of LAK cell therapy is directly related to the numbers of cytotoxic cells infused[1,20].

In contrast, co-culture of the unfractionated lymphocytes with r-HuIFN-γ also results in significant accentuation of the LAK cell cytotoxicity against the tumour targets but this time without

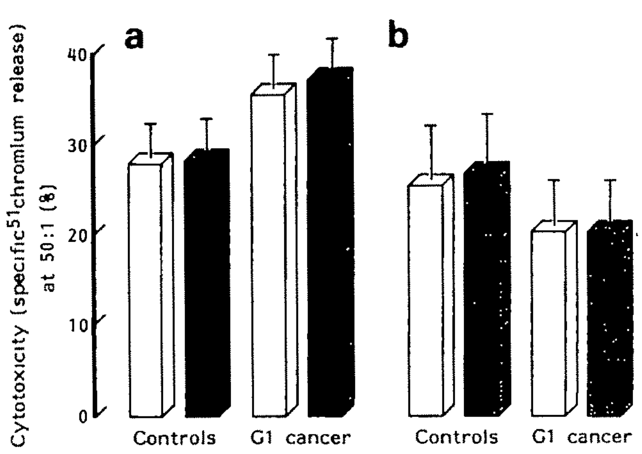

Figure 4 *LAK cell activity of adherent cell depleted mononuclear cells with (▨) and without (□) r-HuIFN-γ in controls and gastrointestinal cancer patients against* **a** *the DAUDI tumour target (controls* n = *8, n.s., cancer patients* n = *11, n.s.),* **b** *the COLO 320 tumour target (controls* n = *6, n.s., cancer patients* n = *10, n.s.)*

the loss of cells during the processing (*Figure 3*). Using this manoeuvre the degree of cytotoxicity generated in the lymphocytes of gastrointestinal cancer patients still does not attain that seen with the lymphocytes obtained from healthy control subjects. However, we would suggest that, of the two procedures, co-culture with r-HuIFN-γ rather than adherent cell depletion is the preferable one for the generation of the maximum number of cells with optimum cytotoxicity for LAK cell therapy in these patients.

Interestingly, by combining these two manoeuvres by co-stimulating adherent cell depleted cells with r-HuIFN-γ we have been unable to augment LAK cell activity further in either of our study groups. There may be several explanations for this. One is that there is a maximal level of LAK cytotoxicity which can be achieved for any given lymphocyte population. Alternatively, it may suggest that r-HuIFN-γ is acting upon a population of mononuclear cells which is removed by plastic adherence. Interferon-γ is known to activate macrophages to become cytotoxic towards tumour cells under certain conditions in patients with colorectal cancer[21]. Moreover it has very recently been reported that interferon-γ can stimulate the expression of interleukin 2 receptors on monocytes[22] and that monocytes can also be activated to become cytotoxic towards epithelial tumour cells on exposure to interleukin 2 (Reference 23). Whatever the mechanism, all the evidence points towards the conclusion that the inclusion of interferon-γ in the stimulation of unfractionated peripheral mononuclear cells with interleukin 2 results in the activation of a further cell population which may not be a lymphocyte (and may well be a monocyte) and which is eliminated during the removal of adherent cells from the total peripheral leukocyte fraction. Such cells, which lose their capacity for plastic adherence over 2 or 3 days in culture, have obvious theoretical implications for adoptive cellular immunotherapy in so far as they represent a further source of cytotoxic cells.

The successful clinical application of adoptive cellular immunotherapy with LAK cells and interleukin 2 has, over the past 3 years, raised a multitude of questions with regard to the optimum protocols which should be utilized. Having developed the maximum cytotoxic capacities of the patients' lymphocytes by use of manipulations such as those we have described here, attention should now be directed towards such factors as increasing tumour cell susceptibility, and the timing of this treatment. Logically this approach should be exploited when the tumour burden is minimal, whenever tumour cells may be displaced to metastatic sites, or when host defences are potentially impaired. This triad of circumstances occurs in the peroperative and postoperative period and thus the potential of this therapy merits detailed investigation in the surgical domain.

Acknowledgements

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Effect of LHRH agonist, Zoladex, on ovarian histology

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In a phase 1 clinical trial Zoladex was used as first line hormonal therapy in premenopausal women with advanced breast cancer. Patients on progression of their disease underwent surgical oöphorectomy. The histology of ovaries from 23 women treated with Zoladex has been compared with the ovaries from 34 patients who, before the clinical trial of Zoladex, underwent surgical oöphorectomy as primary therapy. Both groups show similar follicular phase development. Only 13 per cent of the Zoladex group developed corpora lutea while 58 per cent showed evidence of luteinization in the primary oöphorectomy group ($P<0{\cdot}01$). *Non-neoplastic follicular cysts were seen more often in the ovaries of the Zoladex treated patients than in the primary oöphorectomy group* ($P<0{\cdot}05$). *Zoladex appears to arrest not folliculogenesis but follicular maturation with inhibition of ovulation, the follicles subsequently undergoing atresia with follicular cyst formation.*

Keywords: LHRH agonist, ovarian histology

The endocrinological and clinical effects of the luteinizing hormone releasing hormone (LHRH) Zoladex (ICI PLC, Macclesfield, Cheshire, UK) in premenopausal patients with advanced breast cancer have been reported[1,2]. There have now been proposals to use LHRH agonists as adjuvant therapy in breast cancer and in benign diseases. It is believed that LHRH agonists will offer safe and reversible ovarian suppression, inducing a state of pseudomenopause. Should this be the case these agents could have a major impact in the treatment of a wide range of conditions from benign breast disease to gynaecological disorders.

LHRH agonists initially lead to a substantial rise in the plasma concentrations of gonadotrophins but, with continued administration, secretion of gonadotrophins is diminished and thus is associated with a decline in the circulating concentration of both oestrogen and progesterone. This 'desensitization' to administered LHRH appears to disturb ovulation. There is strong evidence that the primary antifertility effect of long-term LHRH agonist therapy is anovulation[3,4]. We have studied the effects of Zoladex therapy on the histopathological features of ovaries.

Patients and methods

All patients selected for study were premenopausal and had histologically proven locally advanced breast cancer or metastases confirmed by skeletal survey and isotope scans. Menopausal status was established either by a history of regular menstrual cycles or serum follicle stimulating hormone (FSH) levels.

The histology of 68 ovaries from 34 patients who underwent surgical oophorectomy as primary therapy were compared with 39 ovaries from 23 women treated with Zoladex as first line hormonal therapy. These patients had been entered in a phase 1 clinical trial of Zoladex and, on progression of their disease, underwent surgical oophorectomy[2] No patient had received previous endocrine or cytotoxic treatment. Zoladex was administered by daily subcutaneous injection to 19 patients and by monthly depot formulation to 4 patients. Treatment was commenced in the follicular phase of the menstrual cycle. The mean treatment period with Zoladex was 4 months (range 2 weeks–17 months)

Histology

After surgical resection, the ovaries were fixed for 24 h in phosphate buffered formalin The ovaries were examined in the fixed state and from one to three blocks were sampled from each ovary These tissue blocks were processed routinely into paraffin wax and 4-μm sections cut. These were stained with Ehrlich's haematoxylin and eosin.

The ovarian sections were reviewed by one pathologist (I.O.E) and the following features were recorded: the presence of a corpus luteum or corpus albicans, the appearance of the ovarian stroma, the presence of follicular (non-neoplastic) cysts, the presence of neoplastic epithelial lesions, and the presence of secondary tumour. The size of secondary and Graafian follicles and follicular cysts and the frequency of a particular feature were not recorded

Results

The histological features of the ovaries of patients who had undergone oöphorectomy as primary therapy were compared with those having oöphorectomy after Zoladex therapy. Each patient's ovaries were scored for each histological feature and the results are summarized in *Table 1.*

It can be seen that there is no significant difference between the two groups in the histological features of follicular maturation up until ovulation. However, when the ovaries were examined for evidence of a recent luteal phase, 19 of the 34 patients in the primary oöphorectomy group were found to have a corpus luteum histologically, whereas only 3 of the 23 patients

Table 1 *Comparison of histological features seen in primary oophorectomy and Zoladex treated patients on examination of their ovaries*

Histological feature	Primary group oophorectomy ($n=34$)	Zoladex group ($n=23$)	χ^2 (1 d.f.)
Primordial follicles	18	13	n.s.
Primary follicles	9	5	n.s.
Secondary follicles	3	4	n s.
Graafian follicles	4	1	n s
Corpus luteum	19	3	10·6 ($P<0{\cdot}01$)
Follicular cysts	17	18	4·62 ($P<0{\cdot}05$)
Metastatic tumour	10	9	n s.
Normal ovarian stroma	30	22	n s.
Hyalinized stroma	0	1	n.s.
Ovaries entirely replaced by:			
Primary tumour	1	0	n.s.
Secondary tumour	3	0	n.s.

n.s., Not significant

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in the Zoladex group had histological evidence of a recent luteal phase ($P<0{\cdot}01$).

The endocrinological data on these three Zoladex patients have been reviewed. One patient was on Zoladex for only 1 month; no comment would be made regarding adequate endocrinological suppression after only one month of therapy A second patient was on Zoladex for 2 months during which period serum FSH and oestradiol remained unsuppressed. The third patient was on Zoladex for 2 months and appeared to be suppressed.

We further examined the presence of follicular cysts in each group of ovaries. Follicular cysts are derived from atretic Graafian follicles. This histological feature was seen more often in the ovaries of patients treated with Zoladex ($P<0{\cdot}05$).

Metastatic tumour was seen in both groups of ovaries. In the primary oöphorectomy group the ovaries of three patients were entirely replaced by tumour. one further patient in this group was found to have a benign fibroma within one of her ovaries. The remaining 30 patients in the oöphorectomy group had histologically normal ovarian stroma. In the Zoladex treated patients, 22 of the 23 patients had ovaries with normal ovarian stroma, 1 patient had hyalinized stroma. Nine patients in this group had stromal infiltration of metastatic tumour, although none of the ovaries were entirely replaced by tumour. Primary neoplastic lesions were not identified in any case.

Discussion

The postulated modes by which LHRH agonists may exert their effects on the ovaries are disturbed folliculogenesis, inhibition of ovulation, premature luteolysis and/or direct antigonadal effects[5]. There is strong evidence that anovulation is the primary effect of chronic LHRH agonist therapy

Animal studies in hypophysectomized rats have shown that follicular growth can occur up to the size of the largest non pre-ovulatory follicles in the total absence of gonadotrophins[6,7]. However, this class of follicles requires elevated levels of FSH in the cycling rat in order to continue to develop. In the Zoladex treated patients, who have very low levels of circulating gonadotrophins, the ovaries showed histological features of follicular maturation comparable to that seen in the primary oöphorectomy group. However, ovulation with subsequent luteinization appears to be inhibited in the Zoladex group. It is known that the corpus luteum appears to require continued gonadotrophic support for normal function[8]. Premature luteolysis has been induced by administering a LHRH agonist in the mid-luteal phase in normally cycling women[9,10]. Direct gonadal effects of LHRH agonists have been postulated but most evidence suggests that these agents act on the pituitary and not the ovary: this is supported by the previously reported endocrinological data on the Zoladex patients in this study which showed low serum gonadotrophin levels due to desensitization of the pituitary and, as a result, castrate levels of oestradiol and progesterone[1,2].

In conclusion, the results of this study concur with the strong body of evidence that Zoladex prevents ovulation, suggesting that the low levels of serum gonadotrophins in treated patients prevents follicular growth to a mature pre-ovulatory follicle. As a consequence of the inhibition of ovulation, the follicles thus formed can be presumed to undergo atresia with subsequent follicular cyst development. As folliculogenesis continues up to the point of ovulation, while patients are on Zoladex, it may be expected that if therapy is stopped ovulation would recommence and the patient again become fertile.

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Surgical Research Society abstracts

Capillary function in patients with chronic venous insufficiency

P.D. Coleridge Smith and J.H. Scurr, *University College, The Middlesex Hospital School of Medicine, London, UK*

It has been demonstrated in normal subjects that persistently raised venous pressure results in trapping of leucocytes in the peripheral circulation[1]. It is proposed that these cells remain within capillaries and cause occlusion of the lumen. This may be responsible for the perfusion defect that causes the tissue hypoxia associated with venous ulceration

We have studied the blood flow through capillary loops in the skin of patients with normal legs, and those with chronic venous insufficiency with active and healed ulcers. We used capillary video microscopy to determine the number of capillary loops per unit area 5 cm proximal to the medial malleolus. Patients were examined in the supine position at 22°C, and 20 per cent relative humidity. Microscopy was performed after the legs had been dependent for 30 min, then after resting with the feet elevated for 30 min, and finally after sitting with the feet dependent for a further 30 min. Counts of capillary loops were made in all groups The results of those patients with chronic venous insufficiency are shown in the table

Time of examination	Initial dependency	After elevation	After dependency
Median number of capillary loops/mm^2 (range)	3·9 (2·2–7·0)*	5·6 (2·8–12·3)*	5·0 (2·2–9·8)

* $P=0\cdot002$ (Wilcoxon paired rank test)

There is a significant increase in the number of functional capillary loops on elevation of the leg, with a fall on dependency These results support the hypothesis that leucocyte trapping occurs within capillaries and may be responsible for the perfusion defect in chronic venous insufficiency.

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Prognostic features of screening detected colorectal tumours

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Two hundred and seventeen patients have been diagnosed as having colorectal cancer within the test and control groups of a faecal occult blood screening study for colorectal cancer. In the test group there were 55 screen detected tumours (SDTs) and 60 in those who had refused screening Sixteen tumours presented symptomatically in patients who had had a negative test. In the control group 86 tumours have been diagnosed.

Of the SDTs, 30/55 (55 per cent) were Dukes' Stage A compared with 17/162 (10 per cent) of non-screen detected tumours (NSDTs) ($P<0\cdot001$). One out of 55 (2 per cent) SDTs were associated with hepatic metastases compared with 46/162 (28 per cent) NSDTs ($P<0\cdot001$). Ten out of 55 (18 per cent) SDTs were pedunculated polyps treated by colonoscopic polypectomy compared with 2/162 (1·2 per cent) NSDTs ($P<0\cdot001$) The mean size of SDTs was 32 mm compared with 47 mm for NSDTs ($P<0\cdot001$) Fourteen out of 46 (30 per cent) SDTs were histologically well differentiated compared with 11/118 (9 per cent) NSDTs ($P<0\cdot001$). Four out of 48 (8 per cent) SDTs were fixed compared with 38/98 (39 per cent) NSDTs ($P<0\cdot001$). Only 1/55 (2 per cent) SDTs required emergency treatment compared with 31/162 (19 per cent) for NSDTs ($P<0\cdot001$)

Although overall benefit from population screening must be judged by long-term mortality, those patients with screen detected tumours have better prognostic factors

A rational basis for the management of ductal carcinoma in situ of the female breast

R. Carpenter, N.M. Gibbs, J. Matthews, P.D. Boulter and T. Cooke, *Charing Cross Hospital, London, Royal Liverpool Hospital, Liverpool, and Guildford Screening Project, Guildford, UK*

At Guildford, ductal carcinoma *in situ* (DCIS) comprises 15 per cent of all screen-detected breast carcinomas compared with only 4 per cent of symptomatic cancers. Uncertainty regarding the natural history of DCIS has resulted in confusion in management Clinical and biological behaviour of all such screen-detected lesions has been evaluated and compared with symptomatic lesions

Sections of original biopsies were disaggregated enzymatically and Feulgen stained Ploidy was assessed by microdensitometry and related to clinical outcome

Thirty-eight DCIS without invasion detected by screening over 7 years, 19 (50 per cent) were aneuploid compared with 16 symptomatic DCIS with associated microscopic invasion of which 15 were aneuploid Ten non-invasive DCIS (mean diameter 34·1 mm) were treated by mastectomy and 28 by biopsy with a significantly smaller mean diameter of 16·1 mm ($z=3\cdot01$, $P<0\cdot01$)

There have been no recurrences following mastectomy (mean follow-up 4·4 years). Five lesions treated by biopsy have recurred at a mean of 2·6 years, one as invasive carcinoma Although there were no clinical or pathological differences between recurrent and non-recurrent groups, all recurrences were originally aneuploid compared with 8 of 23 non-recurrent cases with a significant relationship between ploidy and recurrence ($\chi^2=4\cdot47$, $P<0\cdot05$).

At present tumour ploidy appears to be the only variable that will assess the natural history of these lesions.

Prior renal transplantation does not enhance canine islet allotransplant survival

A.J. Guy, S.M. Griffin and J.R. Farndon, *University of Newcastle upon Tyne, UK*

Rats bearing long surviving renal allografts subsequently accept islet allografts from the original donor strain without further immunosuppression and show reversal of diabetes[1] The clinical feasibility of such sequential renal and islet transplantation (tx) has been investigated in a large experimental animal, the pancreatectomized dog. Between 11½ and 15 weeks after renal allotransplantation eight dogs underwent pancreatectomy and intrasplenic tx of islets from the original kidney donor Cyclosporin $20\,\text{mg kg}^{-1}\,\text{day}^{-1}$ was started prior to renal tx, the dose being adjusted after islet tx to maintain the plasma cyclosporin concentration above $400\,\text{ng ml}^{-1}$ Six similarly immunosuppressed dogs underwent islet allotransplantation alone

	Graft survival (days)	Total survival (days)
Sequential islet tx	4, 4, 7, 9, 12, 14, 18, 73	6, 9, 11, 13, 13, 20, 24, 73
Islet tx alone	22, 35, 41, 56, 64, >182	27, 47, 48, 71, 79, >182

Both graft and total survival times of sequentially transplanted dogs were less than those of similarly immunosuppressed islet

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allotransplanted animals ($P<0{\cdot}05$ and $P=0{\cdot}01$ respectively, Mann–Whitney U test).

In this model of diabetes, prior donor specific tissue transplantation has an adverse effect upon subsequent islet graft survival, suggesting that the immunological manipulation reported in rodents may not be applicable in clinical islet transplantation.

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Interstitial laser hyperthermia—studies in the normal liver

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The treatment of hepatic tumours is difficult and may often only be palliative. Low power laser interstitial hyperthermia is a precise method of delivering potentially destructive energy to these tumours. In the rat liver, thermal lesions can be produced up to 1·6 cm in diameter that heal by regeneration[1].

In canine liver, coalescing thermal lesions were reproducibly produced with 1·5 W power for 670s (total energy = 4000 J); the gap between each of the four inserted fibres was 1·5 cm. Immediately after irradiation this measured 7 × 4 cm At 1 week mean lesion diameters were 3·5 × 3·0 × 2·7 cm, and at 30 days 2·9 × 1·6 × 2·2 cm. There was one abscess out of 11 lesions made Intra-operative ultrasound allowed precise placing of fibres, imaging of creation of thermal lesions, and accurate measurement of the area of liver affected. Thermometry confirmed that thermotoxic temperatures (55°C) were reached in the region between the four fibres

With this technique thermal necrosis of the liver of a volume comparable to that of human liver tumours can be reproducibly made, with little morbidity. It may provide a useful alternative to major resectional surgery.

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A controlled trial evaluating propranolol in the prevention of recurrent variceal haemorrhage

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Propranolol has been shown to reduce portal venous pressure, but clinical trials of its role in the prevention of further variceal haemorrhage in patients with cirrhosis have produced conflicting results. One hundred and twenty-three unselected patients with cirrhosis and endoscopically proven variceal haemorrhage were screened and treated by injection sclerotherapy on day one. If haemodynamically stable after 3 days and fulfilling trial entry criteria, patients were randomized to receive 160 mg of long-acting propranolol (Inderal LA) once a day or matched placebo, and followed for 2 years without additional therapy Study end points were significant further variceal haemorrhage or death.

The 81 patients (mean age 54 years, 32 males) were randomized into two well-matched populations in whom 57 had alcoholic cirrhosis and modified Child's grades were A· 13, B: 30, C: 38. A total of 38 patients received propranolol, of whom 18 (47 per cent) had further haemorrhage, 14 died, 8 had side-effects (2 withdrawals) and 3 failed to complete follow-up. In all 43 patients received placebo, of whom 33 (77 per cent) had further haemorrhage ($\chi^2=7{\cdot}5$, $P=0{\cdot}006$), 19 died, 5 had side-effects (2 withdrawals) and 5 failed to complete follow-up. In this study propranolol reduced the incidence of late recurrence of variceal haemorrhage in patients with cirrhosis.

Mechanisms for the intracellular accumulation of sex steroids: evidence from breast tumour samples and tissue culture

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Levels of sex steroids presented to their receptors inherently determine activation of the receptor There has been recent evidence of high local concentrations of sex steroids within breast tumours[1]: the mechanism for this is unclear. To investigate this, levels of intracellular steroids (by radioimmunoassay) and intracellular sex hormone binding globulin (i-SHBG) (by the two-tier column method[2]) were measured in benign and malignant breast tissue with the following results.

Steroid (nmol/ng soluble protein)	Malignant breast $n=12$	Normal breast $n=11$	P value
Oestradiol	11 (6·6)	3·3 (1·8)	<0·001
Testosterone	15·1 (12·3)	1·2 (0·54)	<0·001
Dihydrotestosterone	13·3 (7·6)	0·52 (0·24)	<0·0001
SHBG (nmol DHT bound per mg soluble protein)	82 (29·7)	11·5 (0·24)	<0·0001

Statistical tests of difference by Wilcoxon test

The above table confirms the high intracellular sex steroid levels which occur in association with i-SHBG, however, this could be artefactual To investigate further the role of SHBG in breast cancer cells we assayed i-SHBG in MCF-7 cells, using the two-tier assay again and with estimation of oestrogen and androgen the following results were obtained (units of fmol ligand bound per mg of soluble protein)· i-SHBG 32; oestrogen 57; androgen 1.

These results confirm that SHBG can be manufactured within breast carcinoma cells and represents a mechanism for the accumulation locally of sex steroids aiding the tumour autonomy.

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2 Iqbal MJ. A microassay for the determination of binding parameters of oestrogen and androgen receptors employing affinity immobilisation on blue gel. *Anal Biochem* 1985; 144: 79–85.

Xenogeneic islet transplantation in the diabetic nude (athymic) rat

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Current methods of assessing viability of isolated human pancreatic islets utilize *in vitro* techniques A method of assessing *in vivo* function would be a useful adjunct in the evaluation of islet viability following isolation and storage. The nude (athymic) rat offers such a potential model.

In this study we have transplanted nude rats with xenogeneic (mouse) islets 48 h post-induction of diabetes, and have used the renal subcapsular space to allow for subsequent graft removal.

Fifteen nude rats were given streptozotocin (70 mg/kg) intravenously and 14 became diabetic (blood glucose > 20 mmol/l) within 48 h. Seven control animals lost weight (0·5 ± 0·2 g/day) and remained diabetic until death (mean survival 23 ± 1·8 days). Diabetes was reversed within 48 h in 7/7 animals transplanted with 500–750 mouse islets These animals remained normoglycaemic, gained weight (mean 1·9 ± 0·3 g/day) and during glucose tolerance testing showed near-normal response. Graft removal resulted in reversion back to the diabetic state in all animals Histology of the grafts confirmed the presence of islet tissue with no evidence of rejection.

In conclusion, diabetes has been successfully reversed in the diabetic nude rat by xenogeneic islet transplantation. This model offers a potential method for assessing *in vivo* function of isolated human islets

Action of endotoxin on neutrophil and monocyte complement receptors in man

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The activation of circulating phagocytes by endotoxin was studied. Endotoxin (specifically LPS E coli 026:B6) was added to peripheral blood neutrophils and monocytes. Indirect specific immunofluorescence of monoclonal antibodies for the complement receptors for C3b (CR1) and iC3b (CR3), YAZ-1 and OKM-1, respectively, was measured by flow cytometry[1] Results showed that endotoxin activated both cell types in a dose-dependent manner as reflected by massive increases in CR1 and CR3 expression (*Table*). While neutrophil receptor upregulation was greater, monocytes responded faster (2 *versus* > 10 min) and were more sensitive. This action of endotoxin was shown to be independent of complement activation or prostaglandin release. Pretreatment of endotoxin with polymyxin B sulphate, which binds to the lipid A portion of endotoxin reversed the CR1 and CR3 upregulation of both cell types in a dose-dependent manner. Monocyte sensitivity to endotoxin may point to a preferred clearance pathway The action of endotoxin on the neutrophil was shown to produce a dose-related inhibition of chemotaxis to Zymosan activated serum, a source of c5A. These data suggest that endotoxaemia activates and may cause important functional alterations in circulating phagocytes.

Table *Fluorescence (mean channel)*

		LPS (g/ml blood)					
		None	10^{-12}	10^{-9}	10^{-8}	10^{-7}	10^{-5}
Neutrophil	CR1	51	53	48	379	575	640
	CR3	56	55	53	292	645	737
Monocyte	CR1	65	68	213	240	243	400
	CR3	72	79	163	272	291	413

1 Fearon DT, Collins LA. Increased expression of C3b receptors on polymorphonuclear leukocytes induced by chemical factors and by purification procedures *J Immunol* 1983; **130**. 370–75.

Variability of antipneumococcal antibody production to different pneumococcal antigens

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The pathogenesis of pneumococcal postsplenectomy sepsis is poorly understood and prevention of infection is not guaranteed by vaccination. Female New Zealand White rabbits having either a splenectomy or a sham laparotomy have been exposed to Type 2 and Type 3 *Streptococcus pneumoniae* by aerosol inhalation to stimulate naturally acquired infections.

Specific serum IgG antibody responses have been measured by enzyme-linked immunosorbent assay for 3 weeks following infection. The table shows the IgG antibody responses expressed as multiples of pre-exposure levels after 21 days (1·00= no change).

	Type 2 pneumococcus		Type 3 pneumococcus	
	Sham laparotomy ($n=9$)	Splenectomy ($n=9$)	Sham laparotomy ($n=8$)	Splenectomy ($n=7$)
Geometric mean	1·58	1·17	2·78*	1·79
Range	0·71–6·44	0·79–2·20	0·68–14·92	0·68–4·04

* Statistically significant rise $P<0{\cdot}05$ Wilcoxon signed rank test

The results indicate that there was only a significant response in sham-operated animals exposed to Type 3 pneumococcus. This response was abolished in the splenectomized group. Neither group exposed to Type 2 pneumococcus responded significantly The results suggest that splenectomy abolishes specific responses to some strains of *S pneumoniae*; therefore, immunization after splenectomy may be ineffective. Some species do not stimulate a response and therefore immunization against multiple strains may be only partially effective in producing significant circulating levels of IgG.

Simplified isotope detection of occult sepsis

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Leucocytes labelled with indium-111 accurately diagnose abdominal abscess, but cell-labelling facilities are not available in most hospitals and delay in localizing sepsis remains the main cause of mortality *In vivo* cell labelling has been investigated in rodents[1], and we evaluated promising substrates in a chronic abscess model in large mammals.

A 32 cm^3 intra-abdominal sponge containing autologous blood was injected with mixed colonic bacteria in 40 pigs on prophylactic antibiotics[2]. After 2 weeks, ^{111}In-tropolone, ^{111}In-lactoferrin, ^{111}In-fragmented platelets (FP) or ^{111}In-mixed leucocytes were infused in 10 pigs each and gamma scans performed at 4, 24 and 48 h The abscess and critical organs that limit radiation dose were then excised and radioactivity measured in a well crystal.

	Percentage injected activity per 100 g tissue			
	^{111}In-leucocyte	^{111}In-lactoferrin	^{111}In-tropolone	^{111}In-FP
Abscess	1·0±0·1	0·1±0·03*	0·4±0·05*	0·2±0·02*
Spleen	15·0±1·2	2·0±0·3*	1·1±0·07*	5·0±3·1
Liver	4·8±3·0	9·9±0·9*	3·8±0·2*	6·7±0·7

Results mean ± s.e.m. * $P<0{\cdot}01$ Mann–Whitney U test

Isotope uptake in the abscess was greatest with ^{111}In-leucocytes but was adequate for positive scans in all animals given ^{111}In-tropolone. Radiation dose to the spleen (critical organ) was markedly lower with ^{111}In-tropolone at 1·86±0·09 rad/MCi, compared with 11·42±0·82 rad/MCi for mixed leucocytes ($P<0{\cdot}001$). The hepatic dose was also significantly lower with ^{111}In-tropolone but background muscle activity was slightly higher.

Intravenous ^{111}In-tropolone achieves abscess imaging with reduced radiation dose to critical organs. Although sensitivity may be slightly reduced this substrate is easily available and directly administered

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Membrane permeability in hyperdynamic sepsis

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Muscle membrane potential and intracellular electrolytes have been extensively investigated in low flow, hypodynamic shock models, but the information in clinically relevant sepsis models is sparse. The role of altered membrane function in sepsis has been studied using a Ling electrode in Wistar rats following caecal ligation and puncture which produces hyperdynamic sepsis Muscle membrane potential and sodium have been compared with changes in plasma and the red cell sodium at 0, 6, 12 and 18 h after caecal ligation and puncture.

	Time			
	0 h	6 h	12 h	18 h
Muscle membrane potential (mV)	−90·9	−89·1	−80·2*	−69·9*
Intracellular sodium (mmol/l)	6·7	8·3	11·58*	13·95*
Plasma sodium (mmol/l)	141	141	140	142
Erythrocyte sodium (mmol/cell) $\times 10^{-14}$	2·18	2·43	2·54	2·76**

* $P<0{\cdot}01$; ** $P<0{\cdot}05$ (compared with 0 h)

The results suggest a significant muscle membrane depolarization as early as 12 h when the animal is still in a hyperdynamic non-shocked state. Plasma sodium concentration did not change during the study period Red cell sodium is significantly altered only at 18 h Altered plasma membrane function is an early feature of hyperdynamic sepsis and this membrane 'failure' does not result in hyponatraemia. Altered red cell sodium concentration is a late indicator of this membrane failure.

The effect of oral bile salts on serum endotoxin and renal function in obstructive jaundice

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Without prophylaxis acute renal failure is a major factor in postoperative deaths in up to 50 per cent of jaundiced patients[1]. Renal function was assessed pre- and 3 days postoperatively in 38 obstructive jaundice patients and 12 controls. Twelve of the obstructive jaundice group received oral bile salts in the form of sodium deoxycholate (500 mg t.d s.) for 48 h prior to operation Renal function was assessed by creatinine and β_2-microglobulin clearance, from which a sieving coefficient[2] was derived Serum endotoxin was measured using a spectrophotometric method[3] in five of the controls and all of the jaundiced patients. Jaundiced patients who did not receive oral bile salts ($n=26$) had a significant rise in serum endotoxin levels postoperatively (45 ± 7 pg/ml *versus* 65 ± 6 pg/ml, $P<0{\cdot}05$). While the bile salt group ($n=12$) did not have a significant rise in endotoxin levels (51 ± 8 pg/ml *versus* 53 ± 7 pg/ml), they did have significant renal impairment reflected in a fall in creatinine clearance (127 ml *versus* 71 ml/min, $P<0{\cdot}05$) and rise in sieving coefficient (0·78 *versus* 1·35, $P<0{\cdot}01$). There was no correlation between the change in endotoxin levels and change in sieving coefficient in the pre- and postoperative period in any group. We conclude that while bile salts prevent a significant increase in endotoxin levels in the postoperative period in jaundiced patients, they appear to cause proximal tubular impairment.

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Immunorestorative effect of obstructive jaundice after operative injury

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Both operative trauma and obstructive jaundice depress cellular immunity. We compared their effect and interrelationship with surprising results.

Seven groups of Sprague-Dawley rats (unoperated controls and six experimental groups. rats whose common bile ducts were divided (CBD) and rats after laparotomy (LAP) tested at 1, 2 and 3 weeks respectively) were sensitized on the abdomen and subsequently challenged on the ear with dinitrofluorobenzene Percentage ear thickness swellings, measures of delayed hypersensitivity response, were calculated from pre- and post-challenge micrometer measurements. The mean percentage ear thickness increase ± s e.m for each group is shown in the table

	Weeks after surgery		
	1	2	3
Control	$19{\cdot}0\pm2{\cdot}16$ ($n=24$)		
LAP	$1{\cdot}75\pm1{\cdot}93$ ($n=16$)	$14{\cdot}64\pm3{\cdot}13$ ($n=14$)	$16{\cdot}9\pm2{\cdot}6$ ($n=16$)
CBD	$8{\cdot}4\pm2{\cdot}83$ ($n=14$)	$6{\cdot}79\pm2{\cdot}02$ ($n=14$)	$8{\cdot}44\pm1{\cdot}63$ ($n=14$)

Delayed hypersensitivity responses were profoundly depressed after laparotomy ($t=5{\cdot}59$), unpaired, $P<0{\cdot}001$) but later recovered, while responses after bile duct division, though low, were far less diminished than after laparotomy However, the bile duct ligated animals had, of necessity, also undergone laparotomies and the degree of immunodepression in this group would be expected to be equally if not more profound than that after laparotomy alone. However, bile duct division instead partially restored hypersensitivity responses after operative trauma. Ablation of Kupffer cells reverses the immunosuppressive effect of surgery[1] and may underlie the observed immunorestorative effect of obstructive jaundice.

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Enhanced peripheral androgen conversion in patients with hydradenitis suppurativa

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The pattern of endocrine disorder in hidradenitis (HS) suggests an androgenic basis for the disease, but elevated serum testosterone levels are evident in only 15–20 per cent of affected women[1,2]. The end organ (apocrine gland) response to androgens may be of critical importance in this disorder, and has not previously been studied *in vitro*. Biopsies of hair-bearing axillary skin and subdermal fat were obtained from eight women with hidradenitis and four unaffected controls (C). Skin and fat from each subject were incubated separately for 2 h in RPMI 1640 containing NADPH and ^{3}H-testosterone (10^5 d p.m.). 5α-Reductase activities (5αRA) and 5αRA/17β-OH steroid dehydrogenase (17βHSD) ratios were calculated for each sample after extraction and chromatographic separation of testosterone metabolites The results are shown in the table.

Table *Percentage conversion (median) ^{3}H-testosterone to 5α-reduced products per 2 h per 100 mg tissue*

	Controls	Hidradenitis		
Skin	18·6%	24·5%	$P<0{\cdot}05$	Mann–Whitney
Fat	6·1%	29·9%	$P<0{\cdot}01$	

The sensitivity of axillary fat to androgens (5αRA/17βHSD) was significantly greater in samples from hidradenitis patients than controls (HS 8·9 *versus* C 1·7 $P<0{\cdot}01$ Mann–Whitney).

The capacity of apocrine gland laden subdermal axillary fat to transform testosterone into its biologically active metabolites is enhanced in women with hidradenitis. This may be of importance in the production of the occlusive manifestations of the disease

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The mode of action of sulphasalazine and 5-aminosalicylic acid—inhibition of oxygen radical production by neutrophils

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Sulphasalazine (SAL) and its active metabolite, 5-aminosalicylic acid (5ASA), are effective treatment for ulcerative colitis and Crohn's disease. Their exact mode of action is uncertain but may include modification of neutrophil function. We have assessed the effect of SAL and 5ASA on oxygen radical (OR) production by neutrophils *in vitro* in response to two stimuli with different cellular sites of action

Oxygen radical production by neutrophils from healthy volunteers was monitored by luminol dependent chemiluminescence. The initial burst of chemiluminescence in response to chemotactic stimulation with N-formyl-methionyl-leucyl-phenylalanine and cytochalasin B (CP+CB) was markedly inhibited by 50 μM 5ASA ($93\pm2{\cdot}4$ per cent, mean ± s.e.m. percentage inhibition of control response, $n=11$, $P=<0{\cdot}02$) or 50 μM SAL ($69\pm3{\cdot}9$ per cent, $n=8$, $P=<0{\cdot}01$) The

BER 6,

concentration producing 50 per cent inhibition was 3·6±1·8 μM 5ASA mean±s.e.m., $n=6$) and 16·5±6 μM SAL ($n=5$) In contrast, chemiluminescence stimulated by phorbol myristate acetate (PMA) was only weakly inhibited by 50 μM 5ASA (9·8±4 per cent, $n=5$) and 50 μM SAL (28±8·4 per cent, $n=6$)

Inhibition of neutrophil oxygen radical production in response to CP+CB but not PMA by SAL and 5ASA excludes a non-specific toxic effect and implies a specific site of action. These findings support a theory that oxygen radicals are important in the pathogenesis of inflammatory bowel disease.

A new micro-bioassay for prolactin measurement: elevation of the bioactive/radioimmunoassayable prolactin ratio in breast cancer

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Although the role of prolactin (PRL) in rat mammary carcinogenesis is well established, much controversy remains on the role of the hormone in human breast cancer. The results to date have used radioimmunoassays (RIA), which may not necessarily reflect the biological activity of the hormone.

We have modified an existing sensitive bioassay (BA) for PRL and growth hormone[1], based on the mitogenicity of lactogenic hormones for the rat Nb2 lymphoma cell line, to examine prolactin bioactivity in breast disease

Serum PRL levels by both BA and RIA were determined in 31 patients with breast cancer. Basal levels and peak responses to thyrotrophin-releasing hormone (TRH) were evaluated. The BA/RIA PRL ratio was found to be significantly elevated in both basal and TRH-stimulated samples (*Table*).

	Serum prolactin (ng/ml)		Mean BA/RIA ratio
	BA	RIA	
Mean basal level ($n=31$)	10·2	4·7*	2·5
Mean peak TRH level ($n=30$)	68·6	37·0†	2·2

Mann–Whitney *U* test: * $P<0·00001$, † $P<0·001$ BA *versus* RIA

This indicates that variant non-immunogenic forms of the hormone (or enhancing serum factors) may be present, causing increased biological activity. These results suggest that previous attempts to assess the importance of PRL in breast cancer by RIA may have failed to measure the biologically important activity.

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Mastectomy or tamoxifen? A randomized cross-over study in elderly patients with operable breast cancer

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One hundred and thirty-five consecutive patients aged 70 or over with primary breast cancer have been prospectively randomized to receive either wedge mastectomy (simple mastectomy without undercutting of the flaps) or tamoxifen 20 mg b.d. as the initial treatment. Patients randomized to tamoxifen crossed over and had a wedge mastectomy if there was any sign of local progression. Patients randomized to wedge mastectomy were treated with further excision and/or radiotherapy for local recurrence and on failure of these treatments, or on diagnosis of metastatic disease by tamoxifen.

The criteria for entry were: age >70 years, operable breast cancer (maximum diameter 5 cm) and assessed fit for surgery. There was 0 per cent operative mortality in the mastectomy group. There was no significant difference in survival between the two groups.

Complete response was obtained in 44 per cent of the tamoxifen-treated group and partial response in a further 19 per cent. Size was a significant factor in survival in the tamoxifen group in that smaller tumours (<4 cm²) did very well Survival was not related to oestrogen receptor status in the mastectomy groups

Only 35 patients (53 per cent) in the tamoxifen group remain controlled only by tamoxifen compared with 42 patients (65 per cent) in the wedge mastectomy group who were controlled by surgery.

Occult carcinoma and nipple discharge

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Microdochectomy is used to treat single duct nipple discharge We have excised the subareolar major duct system[1] for painless discharge from more than one duct in 68 breasts in 55 patients (median age 52), without galactography Follow-up was for a median 12 months; one required reoperation for recurrent discharge at 15 months

Discharge duration was for a median 7 months. Nipple inversion was present in 17 and palpable abnormalities in 5. Twenty-four cases had bloody, and eight brown/black discharge. Eighty per cent had discharge cytology performed (C0–C5) and ninety-three per cent (xero)-mammography.

Histology revealed a high incidence of occult malignancies (9 per cent), (one infiltrating, and five intraduct carcinomas) and nine duct papillomas (13 per cent). All bloody, brown/black discharge was cytologically benign but included five papillomas, 3 intraduct carcinomas and one invasive carcinoma. No disharge showed atypical (C4) or malignant cells (C5), although five contained suspicious cells (C3: including one papilloma, one intraduct carcinoma)

Twenty-six (xero)-mammograms were normal, thirty-six showed dysplasia and one was diagnostic of intraduct carcinoma

In women over 40 with persistent nipple discharge, 'Hadfield's operation' is therapeutic and diagnostic It should be chosen for a bloody or black/brown discharge, since cytology or (xero)-mammography does not identify occult malignancy but histology detects it.

1 Hadfield GJ. Further experience of the operation for excision of the major duct system of the breast. *Br J Surg* 1968; **55**. 530–5.

Subjective measurements of quality of life predict response to chemotherapy for advanced breast cancer

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To determine whether subjective measurements predict objective response, we have prospectively measured quality of life prior to starting chemotherapy (Epirubicin) for advanced breast cancer Patients completed the following self-assessment questionnaires:

1. *Nottingham health profile* an example of a self-assessment tool designed to measure health status in the community.
2 *Linear analogue scale* (*LASA*) this measures 26 variables The results of the single question 'How do you rate your quality of life?' are shown The clinician awarded scores for

3. *Karnofsky performance status* a crude rating of physical ability
4. *Health index record* another crude categorical scale covering a wider spectrum.

Fifty-four patients are at present assessable using UICC criteria

	Response group			
Test	CR+PR $n=14$	NC $n=30$	PD $n=10$	Significance*
Nottingham health profile	50	115	198	$P<0·001$
LASA	9	7	4·5	$P<0·01$
Karnofsky performance status	90	80	60	$P<0·01$
Health index record	78	70	60	$P<0·02$

CR, complete responders; PR, partial responders; NC, no change, PD, progressive disease. * Trend for subsequent responders to have a higher initial quality of life measurement than non-responders.

Median scores are shown. A high score for the Nottingham health profile indicates a poor quality of life, while for the other tests a high score equates to a good quality of life. The Wilcoxon-type of test for trend described by Cuzick was used for statistical analysis

Even with these crude tests a definite trend was seen with patients who subsequently responded to chemotherapy having a higher initial rating of quality of life. These results indicate that subjective assessments should become an important consideration when deciding whether potentially toxic treatment will benefit the individual.

Abnormalities of coagulation in breast cancer: a prospective study

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Subclinical abnormalities of coagulation and fibrinolysis occur in up to 9 per cent of cancer patients[1], but their significance remains poorly understood. The aim of this study was to define these abnormalities in patients with early breast cancer, and to examine how they relate to eventual prognosis.

Blood was taken pre-operatively from 50 patients with primary operable breast cancer (BC) and from 30 patients with benign breast disease (BBD). These samples were analysed for fibrinopeptide A (FPA), fibrin(ogen) degradation products (FDPs), fragment BB 15–42 (BB 15-42) and fibrinogen Results were compared with age-matched healthy controls by the Mann–Whitney *U* test

Both BC and BBD patients showed very significant elevations of FPA and BB 15-42 compared with healthy controls ($P<0{\cdot}005$) Unexpectedly, there was no significant difference between BC and BBD patients with respect to BB 15-42, and FPA showed only a slight but significant increase in the cancer group ($P<0{\cdot}05$, *Table*). Cancer patients, but not BBD patients, had significantly higher FDPs than controls ($P<0{\cdot}005$)

	FPA (pmol/ml)	BB 15-42 (pmol/ml)	FDPs (μg/ml)	Fibrinogen (g/l)
Breast cancer ($n=50$)	4·1	2·3	2·5	2·9
Benign breast disease ($n=30$)	2·85	2·2	1·875	3·0
Healthy controls ($n=46$)	1·7	1·2	1·25	3·1

Values are medians

Both BC and BBD patients show significant abnormalities of coagulation pre-operatively. These findings may be due to pre-operative 'stress' Non-specific abnormalities of this kind may be partly responsible for the high incidence of coagulation abnormalities previously reported in cancer patients

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Potentiation of oestrogenic stimulation in human breast cancer—a possible explanation for fibroblast mitogenicity

K. Horgan, D.L. Jones and R.E. Mansel, *University of Wales College of Medicine, Cardiff, UK*

Human fibroblasts have previously been shown to stimulate MCF7 human breast cancer growth *in vivo*[1]. Haslam has provided a possible explanation for these results when she demonstrated that the addition of fibroblasts significantly enhanced oestrogenic stimulation of rodent mammary epithelium *in vitro*[2].

We initially determined whether MCF7 human breast cancer tumours produced in nude mice with (MCF7+F) or without (MCF7) the addition of fibroblasts demonstrated increased response to oestrogen as measured by the presence of progesterone receptor activity (prog). The results showed that prog was significantly higher in the MCF7+F group (42 of 53 prog+) than MCF7 tumours (5 of 11 prog+, $P<0{\cdot}05$ χ^2 with Yates' correction). No difference was found in levels of oestrogen receptor Fibroblasts alone were oestrogen receptor negative.

Further studies investigated fibroblast effect on oestrogen independent breast cancer cell lines in non-oestrogen supplemented nude mice. The addition of fibroblasts to inocula of HS578t and MCF7^H ras cells was highly stimulatory for tumour growth. A similar stimulatory effect was found with human melanoma and adrenal carcinoma cell lines.

We conclude from these studies that though fibroblasts may augment oestrogen stimulation in breast cancer the oestrogenic pathway is not the primary mode of action for fibroblast mitogenicity.

1. Horgan K, Jones DL, Mansel RE. Mitogenicity of human fibroblasts *in vivo* for human breast cancer cells *Br J Surg* 1987, 74· 227–9.
2. Haslam, Sandra Z. Mammary fibroblast influence on normal mouse mammary epithelial cell responses to oestrogen *in vitro*. *Cancer Res* 1986; **46**. 310–6.

Predicting response to tamoxifen in advanced breast cancer

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Breast cancer response to tamoxifen cannot be predicted reliably from oestrogen receptor status. Activity of tumour α-glycerol-phosphate-dehydrogenase has been reported to increase following tamoxifen[1]. We investigated the effect of tamoxifen on activity of this and other enzymes involved in lipid biosynthesis: α-glyceraldehydephosphate-dehydrogenase and malic enzyme. Changes in cellular DNA content[2] and thymidine kinase, an enzyme of DNA synthesis under oestrogen control, were also monitored

Needle biopsies of primary breast cancer were assessed for histology, ploidy and enzyme activity before and 6 weeks after commencing tamoxifen. Tumour response was assessed by UICC criteria.

There was a significant reduction in thymidine kinase activity from $5{\cdot}87\pm0{\cdot}95$ to $1{\cdot}98\pm0{\cdot}41$ units/mg protein ($P<0{\cdot}001$, paired *t*) in 10 patients whose disease did not progress over a mean of 4·6 months. In contrast, activity increased from $3{\cdot}43\pm1{\cdot}43$ to $3{\cdot}95\pm1{\cdot}52$ units/mg protein in five patients whose disease progressed (χ^2, $P<0{\cdot}02$). Neither treatment nor tumour progression were related to changes in the other enzymes studied, nor was response related to aneuploid ($n=14$) or diploid ($n=1$) DNA content.

Tamoxifen response was not related to activity of the enzymes of lipid metabolism tested in this study, however, oestrogen-sensitive aspects of DNA synthesis, of which thymidine kinase is an example, appear more rewarding.

1 Deshpande N, Mitchell I, Maltini M, Dimatino L. The effects of the administration of tamoxifen, oestradiol and prednisolone on the activity of certain enzymes of carbohydrate metabolism in primary human breast cancer *in vivo* *Br J Cancer* 1985; **52**: 241–4.
2. Carpenter R, Gibbs N, Matthews J, Cooke T. Importance of cellular DNA content in pre-malignant breast disease and pre-invasive carcinoma of the female breast *Br J Surg* 1987, **74**. 905–6

Anal sensation following restorative proctocolectomy for ulcerative colitis

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High anal pressures were reported after restorative proctocolectomy (RP) with preservation of the entire anal canal (RP+EEA) than after RP with endo-anal anastomosis (RP+EAA)[1] In this study, we investigated the hypothesis that anal sensation might also be better after RP+EEA than after mucosal proctectomy.

Anal sensation was measured in 13 patients before and in 9 patients after RP+EEA. Seven patients who had undergone RP+EAA with preservation of 1 cm of mucosa above the dentate line were also studied. Threshold sensation was measured in the upper, mid and lower anal canal using a bipolar constant current stimulator probe providing square wave stimuli at 100 μs duration and 5 Hz The recto-anal inhibitory reflex was measured and each patient was questioned as to his ability to discriminate flatus from stool and to release flatus without visiting the lavatory.

Anal sensation at each of the three sites did not differ in the three groups of patients (*Table*). The recto-anal reflex was present in all pre-operative patients, in 76 per cent of patients after RP+EEA and in 33 per cent of patients after RP+EAA (n.s.). All patients after RP+EEA, and 63 per cent of patients after RP+EAA, could distinguish flatus from faeces (n.s.). Ninety per cent of patients after RP+EEA and 27 per cent of patients after RP+EAA could 'safely' release flatus ($P<0·01$).

Thus, overall discriminatory function at the anus was better after RP+EEA than after RP+EAA.

Site	Pre-operative (mA)	RP+EEA (mA)	RP+EAA (mA)	*P*
Upper	25·7 (10–34)	23·3 (15–24)	13·1 (10–16)	n.s.
Middle	4·7 (3·9–6·8)	6·4 (3·9–6·8)	3·9 (3·3–4·4)	n.s.
Lower	6·1 (3·8–6·6)	4·4 (3·9–5·6)	4·0 (2·6–4·3)	n.s.

Median Q1–Q3

1. Johnston D, Holdsworth PJ, Nasmyth DG *et al*. Preservation of the entire anal canal in conservative proctocolectomy for ulcerative colitis: a pilot study comparing end-to-end ileo-anal anastomosis without mucosal resection with mucosal proctectomy and endo-anal anastomosis. *Br J Surg* 1987, 74: 940–5

Ras gene abnormalities in large bowel cancer

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DNAs from 31 patients with cancer of the large bowel and from two patients with familial polyposis coli (FPC) were analysed for c-Ha-ras and c-Ki-ras gene abnormalities

Material from colonic tumours and apparently normal colonic tissue was obtained fresh. The DNA was subjected to restriction endonuclease digestion according to the conditions recommended for the individual enzymes (*Bam* HI, *Eco* RI, *Msp*I, *Hpa*II, *Sac*I) and electrophoresed on 1 per cent or 3 per cent agarose gels, depending on the fragment to be identified. The DNA was transferred to a filter—Hybond N and hybridized under stringent conditions to 2×10^8 c.p.m./μg ^{32}P-labelled 6·6 kb Ha-ras DNA from the plasmid pT24C$_3$ or 1·0 kb v-Ki-ras DNA from the plasmid pHiHi overnight. After hybridization the filters were washed and then placed against Kodak XAR5 film at −80°C for 24–48 h using an intensifying screen. A Shimadzu dual wavelength scanner was used to confirm and quantify any differences in band intensity.

Tumour tissue from the FPC patients showed no abnormality. Tumour tissue DNA from 18 of 31 patients showed ras gene abnormalities, largely in the form of amplification. Two tumours with minor amplification of Ha-ras gene also had point mutation at codon 12. There is a correlation between ras gene abnormality and a previous or family history of cancer ($P=0·013$).

Anastomotic materials and colorectal carcinogenesis

J.R. McGregor, D.J. Galloway, Freda Jarrett and W.D. George, *Western Infirmary, Glasgow, UK*

Local recurrence is a major cause of death following curative surgery for colorectal cancer[1]. Because it has been suggested that stapled anastomoses may be associated with an increased incidence of local recurrence, this study was designed to compare the influence of three commonly used anastomotic materials, including steel, on colorectal carcinogenesis.

Male Swiss Albino rats received 12 consecutive weekly subcutaneous injections of azoxymethane (10 mg kg^{-1} week^{-1}. Four weeks after the final injection, half the animals in each group had a 2 cm longitudinal colotomy performed on the antimesenteric border of the distal descending colon This was repaired with eight interrupted transmural 5/0 sutures of either polyamide (Nurolon, Ethicon Ltd , UK), polyglycolic acid (Dexon, Davis and Geck), or stainless steel. The remaining animals had simple transmural implantation of the same number of sutures over the corresponding area of colon Animals were killed 12 weeks postoperatively and the distribution of colonic tumours assessed.

Table *Animals with colonic tumours*

	Suture implantation			Colotomy and re-suture		
	n	Perianastomotic	Remaining colon	*n*	Perianastomotic	Remaining colon
Polyamide	11	7†	6	10	8*	6
Polyglycolic	10	8‡	6	11	10†	4
Steel	10	0	4	10	3	4

* $P<0·05$, † $P<0·01$, ‡ $P<0·001$ compared with steel; Fisher's exact test

In marked contrast to previous reports of enhanced carcinogenesis with steel sutures[2], these results suggest that stainless steel sutures may be associated with significantly fewer perianastomotic tumours than more conventional suture materials.

1. Hurst PA, Prout WG, Kelly JM, Bannister RT, Walker RT Local recurrence after low anterior resection using the staple gun. *Br J Surg* 1982; 69: 275–6.
2. Phillips RKS, Cook HT. Effect of steel wire sutures on the incidence of chemically induced rodent colonic tumours *Br J Surg* 1986, 73: 671–4.

Role of suture materials in implantation metastases: an experimental study

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Viable exfoliated malignant cells may be responsible for local recurrence of colorectal cancer[1]. Anastomotic suture materials may have a role in this process if tumour cells readily adhere to the sutures and are then implanted into the colonic wall.

This study was designed to compare tumour cell adherence to four anastomotic materials. A suspension of ^{51}Cr-labelled Mtln3 adenocarcinoma cells (10^7/ml) was injected intraluminally into the caecum of F344 rats. Ten-centimetre lengths of 5/0 polyamide (Nurolon, Ethicon Ltd, UK), polyglycolic acid (Dexon, Davis and Geck), polypropylene (Prolene, Ethicon Ltd, UK), and stainless steel were passed transmurally through the caecum and immediately transferred to a gamma counter for measurement of radioactivity. In addition, 10-cm lengths of each suture were incubated at 37°C with a similarly labelled cell suspension for 90 min After washing in PBS to remove non-adherent cells, radioactivity was counted as before

The number of cells adherent to each material was calculated by comparing the activity with that of a standard labelled tumour cell suspension. The results are expressed as the median and range.

	Cells adhered *in vivo*	Cells adhered *in vitro*
Polyamide	4662 (1722–15513)	3154 (1202–10406)
Polyglycolic	16560 (6135–30731)	7369 (2451–27361)
Steel	1060 (617–3744)	559 (361–1145)
Polypropylene	1797 (736–3716)	459 (245–944)

The braided materials, and in particular polyglycolic acid, adhere significantly more tumour cells than the monofilaments, stainless steel and polypropylene ($P<0·001$; Kruskal–Wallis) This may have implications for colorectal cancer surgery in man

1. Umpleby HC, Fermor B, Symes MO, Williamson RCN Viability of exfoliated colorectal cancer cells. *Br J Surg* 1984; 71: 659–63

Characteristics of smooth muscle response to distension in the human colon

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Surgical pathology can be specific to the proximal colon (PC) or distal colon (DC). We examined smooth muscle response to stretch in *in vitro* colonic muscle strips and using intraluminal balloon dilatations in the *in vivo* colon of patients with transverse colostomies.

In vitro results showed that PC generates active forceful contractions at significantly greater lengths of stretch than DC, both in the longitudinal layer, 2·4 ± 0·15 *versus* 1·8 ± 0·2 times initial length ($P<0{\cdot}001$), and the circular layer, 3·6 ± 0·3 *versus* 2·2 ± 0·1 times initial length ($P<0{\cdot}001$). Longitudinal muscle generated large contractile responses throughout the colon, 91 ± 17 mN/mm^2 in PC and 128 ± 18 mN/mm^2 in DC compared with the significantly weaker circular muscle, 5·5 ± 1·3 mN/mm^2 in PC and 11·8 ± 2·0 mN/mm^2 in DC ($P<0{\cdot}001$). *In vivo* resistance to distension was significantly greater in DC *versus* PC at intraluminal volumes from 40 ml, 34 ± 10 *versus* 25 ± 7 cmH_2O ($P<0{\cdot}02$), to 100 ml, 64 ± 10 *versus* 45 ± 7 cmH_2O ($P<0{\cdot}01$). Repeating *in vivo* studies in the post-mortem colon, representing passive connective resistance, indicated a totally passive DC response to distension compared with a large active muscular PC response.

Results indicate marked differences in response to intraluminal distension in both sides of the colon and may have implications in disease aetiology and suitability for replacement grafting to other sites in the gastrointestinal tract.

Recurrence of colorectal cancer and perioperative blood transfusion—is blood storage time important?

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Several retrospective studies have suggested that perioperative blood transfusion may have a deleterious effect on survival in patients undergoing resection for colorectal cancer. The mechanics involved are still controversial.

We have investigated the possible effect of blood storage time on survival. In a prospective study the mitogenic activity of plasma from 35 patients undergoing surgery for colorectal cancer was measured using the 3T3 fibroblast cell line technique. Transfused patients exhibited a 100 per cent increase in mitogenic activity over pre-operative values compared with no significant change in non-transfused patients.

Samples were taken from stored blood on days 1, 3, 5, 7, 14 and 28 following donation and mitogenic activity was measured. The mitogenic activity increased with storage time to a maximum at 15 days (60 per cent increase).

In conclusion, an increase in mitogenic activity occurs in patients following blood transfusion and in stored blood. This may be a factor responsible for the deleterious effect of transfusion on recurrence in colorectal cancer and perhaps 'fresh' blood if required should be used.

The effect of low anterior resection on the anal sphincters

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Minor difficulties with continence are frequent after low anterior resection (LAR). Intra-operative injury to the internal anal sphincter or its nerve supply may contribute. To study the effect of LAR on the anal sphincter mechanism, anal manometry was performed on 20 patients before and 10 days after LAR. Ten patients were studied again at 6 months after operation. Resting, maximum squeeze and squeeze increment pressures were recorded. Intra-operative manometry ($n=11$) and presacral nerve stimulation ($n=6$) was performed to determine whether peroperative injury to the internal anal sphincter occurred.

Resting and maximum squeeze anal canal pressures were reduced by LAR, and did not recover (*Table*). The squeeze pressure increment did not change. Division of the inferior mesenteric artery, mobilization of the rectum and rectal transection did not affect resting anal pressure, which was reduced after EEA anastomosis (pre 39 ± 4 mmHg, post 28 ± 3 mmHg, $P<0{\cdot}05$, ($n=5$)). Presacral nerve stimulation produced relaxation of the internal sphincter.

	Anal canal pressure (mmHg)		
	Pre-op $n=20$	Post-op $n=20$	≥6 months $n=10$
Resting	67 ± 4	51 ± 4†	44 ± 4†
Squeeze	103 ± 7	78 ± 6†	73 ± 5*
Increment	35 ± 4	27 ± 4	28 ± 5

* $P<0{\cdot}05$ compared with pre-op; † $P<0{\cdot}001$ compared with pre-op

In conclusion, anal sphincter pressures are reduced after LAR. The external anal sphincter and the nerve supply to the internal anal sphincter appear intact. A direct injury to the internal anal sphincter is postulated.

Large bowel cancer: the effect of perioperative blood transfusion on outcome

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There is increasing support for an association between perioperative blood transfusion and poor outcome in cancer patients[1]. The improvement in renal allograft survival after blood transfusion is well accepted and possibly due to an immunosuppressive effect[2]. This has led to the hypothesis that blood transfusion may enhance tumour growth, recurrence and metastasis. The evidence for such an association is inconclusive and it may be an epiphenomenon.

To establish whether there is an association between transfusion and cancer recurrence or survival, we have collected blood transfusion data on 961 patients entered in the Large Bowel Cancer Project (LBCP) who underwent curative resections for large bowel cancer and left hospital alive. The LBCP is a collaborative prospective study involving 94 surgeons and 38 pathologists in 23 hospitals in the UK.

Blood transfusion was more likely to be given for tumours in the rectum and rectosigmoid, Dukes' C and if there was some degree of tumour fixation.

The results of transfused *versus* not transfused are shown in the table.

				Distant metastases		
	$n=961$	Local recurrence n (%)	Distance metastases n (%)	Liver n (%)	Lung n (%)	Other n (%)
Transfused	591	113(19)	98(17)	36(37)*	26(26)*	36(37)*
Not transfused	370	58(16)	62(17)	45(73)	7(11)	10(16)

* χ^2 $P<0{\cdot}05$

There was no difference in the risk of developing a local recurrence or distant metastases in either the 'transfused' or 'not transfused' groups, but the distribution of distant metastases differed. There was no survival advantage for patients in either group.

Data from the LBCP, the largest study to date, do not support the evidence of an association between blood transfusion and poor outcome in large bowel cancer, but caution should be observed before transfusing cancer patients until the results of other prospective studies are available.

1. Burrows L, Tartter PI. Effect of blood transfusions on colonic malignancy recurrence rate. *Lancet* 1982; ii: 662.
2. Woodruff MFA, van Rood JJ. Possible implications of the effect of blood transfusion on allograft survival. *Lancet* 1983; i: 1201–2.

Technetium-labelled red blood cell scintigraphy in the localization of lower gastrointestinal haemorrhage

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Technetium-labelled red cell scintigraphy was used in the investigation of 41 patients with major rectal haemorrhage. Red cells were labelled *in vivo* with ^{99m}Tc pertechnetate (395–590 m Bq) and serial scans (0–36 h) were taken using a large field gamma camera. There were 22 men and 15 women, mean age 71·3 years (range 32–91 years) and 4 children. The mean haemoglobin at presentation was 9·4 g/dl (range 5·4–13·5 g/dl). The mean transfusion rate was 8·2 units (range 3–20 units).

Forty-three scans were performed, of which 31 were positive and 12 negative. In each case the accuracy of the scan in localizing the bleeding site was checked either by independent investigations (colonoscopy and arteriography, $n=16$) or at laparotomy ($n=15$) (*Table*).

		Independent investigations	
		+ve	−ve
^{99m}Tc scan result	+ve	29	2
	−ve	1	11
Total		30	13

Bleeding was accurately localized by the isotope scan in 29 out of 30 cases (sensitivity 97 per cent). In the 13 cases where no bleeding point could be demonstrated, there were two false positive scans (specificity 85 per cent). The investigation had a high predictive value when both positive (94 per cent) and negative 92 per cent).

^{99m}Tc red cell scintigraphy has a high diagnostic yield, allowing pre-operative localization of bleeding sites. It should be used more widely in the investigation of lower gastrointestinal haemorrhage.

Ambulatory anorectal manometry: a new technique for the investigation of anorectal function

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Anorectal investigations are usually performed in unphysiological 'laboratory' conditions. The aim of this study was to record anal manometry in patients free to go about normal daily activities and relate manometric changes to subjective sensory experiences.

Rectal pressure (RP) and mid-anal sphincter pressure (SP) were recorded in 10 normal subjects (M:F 8:2, age 52 years, range 30–71) for a median duration of 2·8 h. Signals from a microtransducer catheter were digitally converted and stored in a portable electronic memory (Digitrapper, Synectics (UK)) for later computer display and for analysis. The conscious appreciation of the presence and passing of flatus was correlated with manometric findings.

Marked spontaneous sphincter relaxations resulting in equalization of RP and SP occurred seven times per hour (3·7–10)*. The sensation of the presence of flatus was associated with a reduction of SP of 35 mmHg (29–50 mmHg)* and a rise in RP of only 8 mmHg (0–15 mmHg)* such that RP⩾SP in 85 per cent of events (SP within 5 mmHg of RP in 92 per cent). Flatus was passed principally by a marked reduction in SP (38 mmHg, 30–55 mmHg)* with a relatively small rise in rectal pressure (7·5 mmHg, 0–27 mmHg)*. This contrasts strongly with results in a 'laboratory' situation[1].

Our study demonstrates the importance of the sampling reflex for sensory discrimination of rectal contents. We have shown for the first time that this is a normal and frequent occurrence in healthy ambulatory subjects.

* Median (quartile range)

1 Finlay IG, Carter K, McCleod I. A comparison of intrarectal infusion of gas and mass on anorectal angle and anal canal pressure. *Br J Surg* 1986; **73**: 1025.

The trophic effects of gastrin on the human gastric cell line MKN 45, in vitro and in vivo

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The recent evidence that the hormone gastrin stimulates growth of gastrointestinal tract tumour cells was further investigated.

The established human gastric cell line MKN45 was evaluated for the presence of gastrin receptors by flow cytometry and found to have a definitive number. However, MKN45 showed no *in vitro* growth response to gastrin as measured by [^{75}Se]selenomethionine incorporation unless thymidine synchronization of the cell population was induced, after which the cells responded trophically (125 per cent of control) to the hormone gastrin.

The same cell line was xenotransplanted into nude mice, the resultant tumours were disaggregated and the cells placed in *in vitro* culture, where upon synchronization they showed an even greater trophic response to gastrin (145 per cent of control), but this response was lost on further passaging.

Such xenotransplants were examined for gastrin dependence *in vivo* and 50–60 per cent of the tumours responded trophically to exogenous gastrin (administered subcutaneously, daily). When the gastrin responsive tumours were retransplanted an overall increase in growth and a greater response to gastrin was achieved. The overall response to gastrin was further improved by administering the compound continuously via a pump.

It is suggested that gastrin receptor antagonists may have a future role in the inhibition of gastric and colorectal cancer growth.

Adjuvant therapy for colorectal cancer using regional 5-FU and starch microspheres

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Degradable starch microspheres (DSM) can be injected through a regional artery with cytotoxic agents to produce higher local concentrations than injection of cytotoxics alone, with less systemic exposure[1]. Since local recurrence occurs in up to 40 per cent of patients having curative surgery for large bowel cancer[2], and systemic cytotoxic administration fails to produce effective concentrations locally[3], we studied the effect of giving DSM (diameter 45 μm) and 5-fluorouracil (5-FU) through the inferior mesenteric artery as a route for adjuvant therapy.

An isolated perfused preparation of human colon was used for experiments. A bolus of 5-fluoro[6-H^3] uracil (500 mg 200 μCi) was injected through the inferior mesenteric artery of eight specimens containing tumours and its distribution determined by scintillation-counting. 5-FU was distributed throughout tumour and adjacent tissues. Radiochromatography of tissue extracts suggested fluorouracil metabolites were present.

Twenty-one specimens were perfused with a solution containing α-amylase. Microspheres ($600\,\mathrm{mg}/6\times10^7$) were injected in suspension with 5-FU, and separately, before and after 5-FU. Tissue concentrations were increased only when microspheres were given after 5-FU ($P<0\cdot05$). There was a 20 per cent reduction in the amount of 5-FU entering veins draining specimens ($P<0\cdot05$). High local concentrations and less systemic exposure could be achieved by injecting 5-FU and DSM through a mesenteric artery before resection, which could reduce local tumour recurrence.

1 Dakhil S, Ensminger W, Cho K, Niederhuber J, Doan K, Wheeler, R. Improved regional selectivity of hepatic arterial BCNU with degradable microspheres. *Cancer* 1982; **50**: 631–5.

2 Pahlman L, Glimelius B. Local recurrences after surgical treatment for colorectal cancer. *Acta Chir Scand* 1984; **150**: 331–5.

3. Drewinko B, Yang L. Cellular basis for the inefficiency of 5-FU in human colon carcinoma. *Cancer Treatment Rep* 1985, **45**. 1391–8.

The comparative value of tissue oxygen measurements and sepsis scoring in determining the outcome of pancreatitis and peritonitis

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Accurate prediction of outcome of peritonitis is possible using scoring of multiple physiological criteria[1], but takes up to 48 h to determine

Subcutaneous tissue oxygen measurement (ScP_{O_2}) takes only minutes to perform and provides a dynamic indicator of physiological performance.

We have compared the APACHE II disease scoring index with subcutaneous and transcutaneous (Tc_{O_2}) tissue oxygen measurements (taken from the anterior chest wall) in 11 patients with pancreatitis or peritonitis. In the three patients who died the APACHE II score was 14:12–24 (median:range) and ScP_{O_2} 42:38–63. The eight survivors had an APACHE II score of 6:2–8 ($P<0{\cdot}01$ Mann–Whitney) and ScP_{O_2} of 69:50–95 ($P<0{\cdot}05$). There was a significant inverse correlation between APACHE II score and ScP_{O_2} ($P<0{\cdot}05$ Spearman rank correlation).

There was no significant difference between Tc_{O_2} or arterial P_{O_2} in survivors (47:42–65 and 65:63–84) and those who died (44:38–65 and 69:29–105).

From these early results we suggest that ScP_{O_2} has the potential for rapid prediction of outcome of pancreatitis or peritonitis which may be as accurate as APACHE II disease-severity scoring, whereas Tc_{O_2} measurements, although useful in other fields, appear to have no value.

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The effects of SMS 201-995 on reticulo-endothelial system activity and pulmonary function in rats with acute pancreatitis

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The aim of this study was to establish whether or not some of the beneficial effects of SMS 201-995 in ameliorating acute pancreatitis are attributable to changes in reticulo-endothelial system (RES) activity or pulmonary function.

Pancreatitis was induced with a common bile duct ligature in male Wistar rats. Twelve hours later a second ligature was placed around the bile duct in the region of the liver hilum. One group of rats received 2 μg SMS 201-995 subcutaneously and a further dose 6 h later A control group was dosed similarly with saline. RES activity was assessed by the hepatic and splenic uptake of ^{99}Tc sulphur colloid (^{99}Tc-Sc) and by circulating levels of endotoxin. Pulmonary function was assessed by lung compliance, lung weight and blood gases.

The establishment of pancreatitis was associated with an impairment of RES activity and pulmonary function. In rats treated with SMS 201-995, RES activity (liver:blood ^{99}Tc-Sc $11{\cdot}9 \pm 1{\cdot}4$; spleen: blood $4{\cdot}2 \pm 0{\cdot}7$) was significantly higher than in controls (liver:blood $0{\cdot}4 \pm 0{\cdot}07$; spleen:blood $0{\cdot}2 \pm 0{\cdot}05$) and endotoxin levels significantly lower (SMS $12{\cdot}3 \pm 1{\cdot}6$, controls $57{\cdot}8 \pm 4{\cdot}8$ ng/l). Pulmonary function was also significantly improved ($P<0{\cdot}05$) in SMS-treated rats (compliance $0{\cdot}83 \pm 0{\cdot}06$ ml cm$H_2O^{-1}g^{-1}$; lung weight per cent body weight $0{\cdot}37 \pm 0{\cdot}02$) compared with controls (compliance $0{\cdot}58 \pm 0{\cdot}06$ ml cm$H_2O^{-1}g^{-1}$, lung weight per cent body weight $0{\cdot}48 \pm 0{\cdot}03$). Pa_{O_2} was significantly higher ($P<0{\cdot}05$) and Pa_{CO_2} significantly lower ($P<0{\cdot}05$) in SMS-treated animals.

These results suggest that some of the beneficial effects of SMS 201-995 in ameliorating established acute pancreatitis may be related to stimulation of RES activity

Dynamic CT angiography—a precise technique for the identification of pancreatic necrosis

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For a small minority of patients with acute pancreatitis (AP), surgical intervention is necessary Selection of patients is dependent upon accurate identification of pancreatic and peripancreatic necrosis. Computed tomography (CT) and ultrasound have proven unreliable[1,2].

The role of dynamic CT angiography, employing 5 mm incremental scanning in 8 s cycles after rapid injection of concentrated non-ionic contrast medium (Niopam-370, Merck) at a dose of 1·5–2 ml/kg, was evaluated in 26 patients with severe AP. Selection criteria were: established multi-organ failure, $n=5$, an increasing APACHE-II score[3] at 5 days, $n=14$; or suspected necrosis from ultrasound or CT prior to referral, $n=8$. The presence of necrosis was established at laparotomy or autopsy.

Pancreatic or peripancreatic necrosis was present in seven cases (diagnosis at laparotomy $n=4$, autopsy $n=3$), and in each there were one or more areas of non-enhancing pancreatic parenchyma. Pancreatic enhancement was considered normal in 19 patients, all of whom survived without laparotomy to remove necrotic pancreas, although 8 were subsequently treated for localized pseudocyst or abscess (percutaneous aspiration $n=4$, laparotomy and drainage $n=4$). Dynamic CT angiography appears to provide precise diagnosis and localization of pancreatic necrosis.

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Mononuclear phagocyte dysfunction in severe acute pancreatitis

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Mortality from experimental acute pancreatitis is increased by suppression of phagocytic cells[1], and diminished by immunostimulation[1,2]. Clearance of circulating, enzymatically active protease-antiprotease complexes is a consequence of specific receptor-mediated endocytosis by mononuclear phagocytes. Delayed clearance of complexes has been demonstrated in severe acute pancreatitis[3], suggesting impairment of phagocyte function. The aim of the present study was to investigate the relationship of phagocyte function to severity of acute pancreatitis (AP). Peripheral blood polymorphonuclear neutrophils and mononuclear phagocytes were isolated by a modification of Boyum's method, and cultured in monolayers. After stimulation with Zymosan-A ($6{\cdot}5 \times 10^6$ particles per 1×10^6 cells), the phagocytic index was calculated as the proportion of cells containing two or more ingested particles. Subjects were healthy controls ($n=8$) and patients with AP studied <24 h after admission to hospital ($n=18$, 11 mild, 7 severe attacks by clinical criteria)

Table *Phagocytic index* (%)

		Monocytes		Polymorphs	
	n	Median	Range	Median	Range
Control	8	26·9	18·3–77·0*	35·8	14·5–91·0
Mild AP	15	20·2	11·8–59·0†	43·6	9·2–82·6
Severe AP	7	4·0	2·2–36·4*†	32·4	10·5–47·1

* $P<0{\cdot}02$, control *versus* severe; † $P<0{\cdot}05$, mild *versus* severe, two-sample rank test

In patients with severe AP, monocyte phagocytosis was significantly impaired compared with controls and patients with mild AP, although polymorph phagocytosis was not significantly different. Defective mononuclear phagocyte function is a potential explanation for delayed clearance of toxic protease-antiprotease complexes in severe AP. Immunomodulating agents which stimulate monocyte function may have a therapeutic role.

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Can fibronectin predict the outcome of acute pancreatitis?

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Low levels of fibronectin have been reported to occur in septicaemia and following major surgery or burn injury. In critically ill patients fibronectin-rich infusions have been reported to improve cardiopulmonary function and tissue oxygenation. We have studied the sequential changes of plasma fibronectin in 25 attacks of acute pancreatitis (24 patients: 20 males, 4 females, mean age 49, range 26–86 years). Aetiologies comprised alcohol (15), gallstones (6) and various causes (4). Two major patterns emerged: 17 patients had a rising (16) or a stable (1) fibronectin pattern throughout their illness. All but one (with respiratory insufficiency) had a mild, uncomplicated clinical course. The other eight patients had a falling fibronectin pattern (6) or subnormal levels on the single samples available prior to their death (2). Of the six with a falling fibronectin pattern, two developed pancreatic necrosis (both died), one developed a pseudocyst, one respiratory insufficiency and two had a mild, uncomplicated attack. Three of the four patients dying had subnormal fibronectin levels.

Fibronectin appears a useful marker of severity in acute pancreatitis, a low or falling pattern predicting a complicated attack in six of eight patients. The apparent benefit from fresh frozen plasma in an uncontrolled study and the anecdotal reports of success with exchange transfusion or plasmapheresis in patients critically ill with pancreatitis might be explained by the effect of repleting plasma fibronectin.

Does urgent endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy in acute gallstone pancreatitis improve outcome?

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Although up to 60 per cent of patients with acute gallstone pancreatitis (AGP) have common bile duct (CBD) stones at the time of death, the role of urgent endoscopic retrograde cholangiopancreatography (ERCP) ± endoscopic sphincterotomy (ES) remains controversial. A prospective randomized study was therefore undertaken to assess these techniques.

Over a 5-year period 131 patients with suspected AGP (serum amylase >1000 units/l) were randomized either to conventional treatment (group A) or ERCP (group B) within 72 h of admission. ES and CBD stone extraction was undertaken only if stones were found at ERCP. Gallstones were diagnosed by urgent ultrasound or biochemical prediction. Patients were prospectively stratified using (modified) Glasgow criteria into mild or severe. Ten patients had alternative aetiologies and were excluded. The results in the remaining 121 patients (*Table*) showed an increased complication rate in group A ($\chi^2=9.35$, d.f. = 1, $P=0.002$).

		Complications			
Group	*n*	Pseudocysts	Systemic	Deaths	Patients with complications
A—mild	34	4	0	0	4 (12%)
B—mild	34	3	1	0	4 (12%)
A—severe	28	8	12	5	17 (61%)
B—severe	25	3	3	1	6 (24%)

There were fewer complications in patients with predicted severe attacks in group B but not in those with predicted mild attacks ($\chi^2=4.93$, d.f. = 1, $P=0.026$).

In conclusion, not only has ERCP/ES been shown to be safe in acute pancreatitis, but the outcome is considerably improved in patients with predicted severe attacks of gallstone pancreatitis. ERCP/ES should be included in the management of these patients.

Does fresh frozen plasma improve survival in severe acute pancreatitis?

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Clinical trials of intravenous fresh frozen plasma (FFP) in acute pancreatitis have been undertaken, attempting to restore declining serum levels of α_2 macroglobulin (α_2M). However, published animal studies suggest that peritoneal α_2M levels correlate better with mortality in severe pancreatitis.

The aim of this study was to determine whether FFP given intravenously (IV) or intraperitoneally (IP) improves survival by altering the serum or peritoneal α_2M levels in a rat model of severe pancreatitis.

Rats were randomly allocated into four treatment groups (21 rats each): (1) IV saline, (2) IV Haemaccel, (3) IV rat FFP, (4) IP rat FFP (Haemaccel acting as a colloid control). At 72 h, surviving rats were killed; blood and ascites were analysed for α_2M trypsin binding capacity (α_2MTBC), a measure of unbound α_2M. The results are shown in the table.

	IV saline	IV Haemaccel	IV rat FFP	IP rat FFP
Survivors	0	8	10	13
Serum α_2MTBC	—	14·8(7–20)	15·8(11–23)	18·0(6–23·5)
Ascitic α_2MTBC	—	5·5(3–10)	7·0(4–12)	10·5(7–16)

Compared with saline, treatment improved survival: IV Haemaccel ($\chi^2=9.88$, $P<0.005$), IV rat FFP ($\chi^2=13.12$, $P<0.0005$), IP rat FFP ($\chi^2=18.83$, $P<0.0001$). The differences between Haemaccel and FFP were not significant.

IV FFP failed to raise serum or ascitic α_2M levels compared with Haemaccel (Mann–Whitney = n.s.). However, IP FFP increased ascitic α_2M levels compared with IV Haemaccel ($P=0.006$) and IV rat FFP ($P=0.03$).

In conclusion IV Haemaccel or FFP improve survival, presumably by colloid replacement. In addition, IP FFP increases peritoneal α_2M levels. Clinically, peritoneal lavage, followed by instillation of FFP would remove enzymes, replace protein and replenish intraperitoneal α_2M

Admission enhanced abdominal CT scan and prediction of severity of acute pancreatitis

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One hundred and twenty-six patients with acute pancreatitis had enhanced abdominal CT scans within 72 h of admission Ninety-two attacks were clinically mild, thirty-four were clinically severe. Pancreatic enhancement was defined as decreased, increased or normal compared with the liver and spleen. The maximum anteroposterior measurement of the head, body and tail were multiplied together to produce a 'pancreatic size index'

The median (range) pancreatic size index for clinically severe attacks was 33·2 cm (4·5–269·0), for mild attacks 13·8 cm (1·0–80·0), $P<0.0001$ Mann–Whitney *U* test. The sensitivities and specificities of various CT signs for clinically severe attacks are shown in the table.

CT sign	Sensitivity (%)	Specificity (%)
Decreased pancreatic enhancement	79	42
Loss of peripancreatic tissue planes	82	45
Pancreatic size index >15 cm	88	51
Pancreatic size index >15 cm + loss of peripancreatic tissue planes	70	67
Decreased pancreatic enhancement + size index >15 cm	71	78

Modified Glasgow criteria had a sensitivity of 85 per cent and specificity of 79 per cent for clinically severe attacks In conclusion, patients with clinically severe attacks had a significantly higher median pancreatic size index on admission No single CT sign could improve on modified Glasgow criteria for prediction of severity, although the addition of pancreatic size index of >15 cm to these criteria increased their specificity from 79 to 88 per cent.

Monoclonal antibody M24 defines parity-related cellular patterns in breast ducts

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Monoclonal antibody M8, M18 and M24 define subsets of human breast epithelial cells. When breast ducts are obtained by microdissection and the binding of these antibodies is investigated using immunofluorescence, interesting two-dimensional patterns are seen We have investigated the relationship between these patterns and clinical status.

Of the 56 patients studied, 44 had breast cancer and 12 had benign conditions. Sixteen of the patients were premenopausal and eighteen were nulliparous Specimens from 50, 44 and 46 patients were stained with M8, M18 and M24 respectively. Fourteen patterns were defined by the three antibodies and two patterns were of special interest.

First, small possibly neoplastic clusters of cells were found in ducts from 27 (71 per cent) breast cancer patients as compared with 4 (33 per cent) benign control patients ($0{\cdot}01 < P < 0{\cdot}05$) However, the ages of these two groups were significantly different, raising the possibility that this pattern was age rather than cancer related.

Secondly, a pattern of dense sheets of cells binding M24 was found in 20 (61 per cent) parous patients as compared with 1 (8 per cent) nulliparous patients ($0{\cdot}001 < P < 0{\cdot}01$). These two groups were well matched for age. This difference is important in view of the protection afforded by pregnancy against the development of breast cancer.

Serum lipoperoxides and thromboxane as markers of graft viability in pancreatic preservation/transplantation

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Cell membranes are vulnerable to ischaemic and oxygen free radical damage. Lipoperoxides, products of membrane lysis, may activate the arachidonate cascade and liberate eucanosoids, influencing microcirculation. This study evaluated these products as predictors of pancreatic graft function after ischaemia

Serum lipoperoxides (TBA method) in addition to thromboxane (radioimmunassay), glucose and glutathione peroxidase were measured 30 min and 24 h after transplantation of pancreas stored in cold Collins solution for varying ischaemic periods Six groups of 10 diabetic Lewis rats (streptozotocine 55 mm/kg), were studied, controls and transplants after 0, 30 min, 6 h, 12 h and 18 h storage. Serum glucose was normal after all transplants except after 18 h storage, which showed non-function.

Control lipoperoxides (0·819 ± 0·027 nm/ml) were not significantly elevated after immediate transplantation or 30 min ischaemia With 6 h and longer cold ischaemia there was a progressive elevation of lipoperoxides (peak 3·525 ± 0·33 nm/ml, 18 h group), significant in the 12 and 18 h groups ($P < 0{\cdot}001$, Student's *t* test). There was no significant change in glutathione levels. Control thromboxane levels (2·7 nm/ml) were elevated after all storage periods and were significantly higher 24 h after transplantation (peak 239·69 ± 20·79 nm/ml, 6 h group) except after 18 h storage, where levels were lower than after immediate transplantation

These results suggest that lipoperoxide products may activate the arachidonate cascade, the resulting thromboxane response helping to maintain microcirculation. When this response is overwhelmed, microcirculatory and graft failure ensue, resulting in lipoperoxides being a possible limiting factor and predictor of function in transplants after cold ischaemia.

Cyclosporin A allows prolonged canine islet allotransplant function

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The effect of cyclosporin A (CsA) on islet transplant survival has been investigated using 27 pancreatectomized beagles in four groups autotransplants (group 1, $n=9$), immunosuppressed autotransplants (group 2, $n=6$), allotransplants (group 3, $n=6$) and immunosuppressed allotransplants (group 4, $n=6$). Single-donor pancreatic microfragment grafts were prepared by collagenase perfusion[1] and transplanted into the splenic pulp. CsA was given by intramuscular injection to dogs in groups 2 and 4 at an initial dose of 20 mg kg^{-1} day^{-1}, adjusted to maintain the plasma CsA concentration above 400 ng ml^{-1}. Plasma glucose and insulin were measured in the post-transplant period.

Results	Group 1	Group 2	Group 3	Group 4
Normo-glycaemia Days	>28 × 3, 91 >182 × 5	26, 42, 49 >84 × 3	2, 3, 4 4, 5, 5	22, 35, 41 56, 64 >182 × 1

CsA treatment did not significantly affect autotransplant survival at 1 or 3 months (Fisher's exact test) Non-immunosuppressed allotransplants were rapidly rejected. CsA treatment significantly prolonged islet allotransplant normoglycaemic survival ($P < 0{\cdot}005$, Mann–Whitney *U* test). Six long-term survivors underwent splenectomy· they all rapidly became severely diabetic, demonstrating unequivocal graft dependence

The use of CsA, monitored to maintain an adequate plasma concentration, has allowed significant prolongation of canine islet allotransplant function

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Renal transplantation: the non-starters

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Primary non-function[1] (PNF) rates in renal transplant recipients vary between 10 per cent and 75 per cent PNF may increase hospital stay, investigations (and associated morbidity), and dialysis in the early postoperative period and is associated with poor long-term graft function[2]. We have prospectively studied possible causes of PNF in 106 consecutive renal transplants. The variables included: first and second warm ischaemia times, cold ischaemia time, donor and recipient ages, blood pressures, urine outputs and HLA and DR match. Immunosuppression, percentage cytotoxic antibodies, dialysis regime, kidney perfusate, transplant number and surgeon operating were also studied prospectively. PNF was defined as the need for dialysis in the first 7 postoperative days. The PNF rate was 57·5 per cent. Two factors were significantly associated with PNF: immunosuppression with cyclosporin (CYA), and a second warm ischaemia (SWI) time of >30 minutes. Using stepwise logistic regression analysis, the most significant independent factor in the development of PNF was, first, CYA ($P=0{\cdot}0117$) followed by the duration of SWI ($P=0{\cdot}0238$) CYA was given in a dose of 15 mg/kg pre-operatively and at 10 mg/kg per day for the first week after transplantation. Those CYA patients ($n=93$) with SWI of <30 minutes had a PNF rate of 50·9 per cent, but those with an SWI of >30 minutes had a PNF rate of 76·3 per cent ($\chi^2=5{\cdot}09$, $P=0{\cdot}028$) No such trend was seen in patients who did not receive CYA, regardless of SWI. These findings suggest that CYA and SWI >30 minutes act synergistically in the aetiology of PNF

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Chemosensitivity of breast cells in secondary cultures

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Little is known about the relative sensitivity of breast carcinoma and 'normal' breast tissue to chemotherapeutic agents, although it is often assumed that breast tumour cells are more sensitive than normal breast epithelium.

In this study, an *in vitro* colony-forming assay has been used to examine the relative sensitivity of breast epithelial cells and breast tumour cells to Adriamycin Paired samples of breast cancer and adjacent 'normal' breast tissue were obtained from 11 women undergoing mastectomy. After collagenase digestion, epithelial cells and organoids were maintained in primary culture as ring colonies Confirmation of the epithelial nature of these cells was obtained by morphology, electron microscopy and staining with antibodies to cytokeratin, lactalbumin and HMFG 1 and 2. After 5 days, proliferating cells were subcultured on to fibroblast feeder cells and the sensitivity to Adriamycin determined by calculation of the drug concentration required to cause 50 per cent colony killing.

There was a 20-fold difference in Adriamycin sensitivity (0·1–2·0 μg) between the most sensitive and least sensitive tumours. However, in all 11 individual patients, there was surprising similarity in the drug sensitivity of tumour and 'normal' epithelial cells.

These findings suggest that the drug sensitivity of individual breast tumours may be a reflection of the drug sensitivity of normal tissues, and that this varies markedly between individuals.

Significance of change in cellular DNA content during the genesis of breast cancer

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There are no histological features which predict the biological behaviour of premalignant and pre-invasive breast lesions increasingly detected as a result of breast screening. We have investigated changes in cellular DNA content, proliferative index (PI) and ploidy during the evolution of carcinogen-induced rat mammary carcinoma.

After intragastric instillation of dimethylbenzanthracene, or saline as control, breast tissue was sampled at 2-weekly intervals, disaggregated, Feulgen stained and PI and ploidy assessed using integrating microdensitometry.

Glandular hyperplasia present in 45 per cent of glands was seen more frequently than in controls by the second week of treatment ($P<0{\cdot}01$). Mean PIs of 7 and 9 per cent were significantly higher in induced breasts at 2 and 4 weeks relative to control values of 4·6 and 3·7 per cent ($P<0{\cdot}04$ and $P<0{\cdot}03$ respectively). Aneuploid profiles, never seen in controls, first occurred at 4 weeks in 33 per cent of glands, rising to a maximum of 54 per cent by 6 weeks. Carcinoma, evident at 6 weeks, occurred in up to 50 per cent of glands, but was preceded by aneuploidy and abnormally high PI in all cases ($r=0{\cdot}86$, $P<0{\cdot}05$ and $r=0{\cdot}98$, $P<0{\cdot}01$ respectively).

In this animal model, quantitative changes in cellular DNA content precede the appearance of carcinoma, indicating the potential benefit of similar assessment of human pre-invasive breast lesions.

Human breast cancer: a retrovirus in peripheral monocytes and breast tissue macrophages

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Although a retrovirus, mouse mammary tumour virus, is one of the known causes of breast cancer in mice, attempts to find a similar agent in human breast cancer have been largely unsuccessful. We have recently shown that reverse transcriptase, an enzyme specific to retroviruses, is present in the supernatant of incubated monocytes from patients with breast cancer[1]. The aim of this study was to investigate whether peripheral monocytes and macrophages in breast cancer tissues contain retroviral particles.

Monocytes were incubated in Eagle's medium for 6 days at 37°C and 5 per cent CO_2. After incubation the culture medium was centrifuged at 600*g* to separate the monocytes. The supernatant was filtered (220 nm) and centrifuged at 100 000*g*. The pellet was resuspended in buffer and negatively stained for electron microscopy.

Tissue from six tumours was collected immediately after mastectomy and the incubated monocytes from these patients were fixed with cacodylate-buffered glutaraldehyde (2·5 per cent v/v), embedded in Araldite and thin-sectioned. Sections were stained with lead citrate and uranyl acetate (2 per cent v/v). Negative stain electron microscopy of the pellet revealed the presence of nucleocapsids (100–120 nm in diameter) with fringed envelope similar to murine mammary tumour virus observed in the culture medium of incubated murine mammary tumour cell line. Electron-microscopic examination of incubated monocytes from patients with breast cancer revealed the presence of particles, near the cell membrane, similar to those observed in a cell line infected with human immunodeficiency virus. Electron-microscopic examination of thin section from breast cancer tissues showed no such particles in breast cancer cells, but macrophages present in these tissues showed particles similar to those observed in monocytes.

These findings strongly support our previous observations which indicate that monocytes from patients with breast cancer contain a retrovirus. The role of this retrovirus in the pathophysiology of the disease remains to be established.

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Neointimal hyperplasia in the rabbit is reduced by α_1-adrenergic blockade

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Endothelial trauma may lead to vessel stenosis through the development of neointimal hyperplasia. These hyperplastic vessels exhibit increased sensitivity to noradrenaline which can be reduced by the α_1 antagonist prazosin[1,2]. As the α_1-adrenergic receptor and platelet-derived growth factor, which promotes vascular smooth-muscle-cell proliferation, act through the same metabolic pathway, we postulated that α_1-adrenergic blockade might reduce the development of neointimal hyperplasia. Twenty-four New Zealand white rabbits underwent endothelial denudation of the aorta using a Fogarty balloon catheter. Half were commenced on prazosin (4 mg PO daily) on the day of surgery and continued until they were killed 1 or 4 weeks later. They were then perfused with glutaraldehyde to fix the vasculature *in situ*. Neointimal hyperplasia in cross-sections of the aorta was measured with an X-Y digitizer and was standardized in terms of percentage luminal reduction. Prazosin-treated rabbits had significantly less luminal reduction at 1 week (0·75 per cent ± 1·8 per cent *versus* 9·7 per cent ± 3·1 per cent, mean ± s.e.m., $P<0{\cdot}001$) and at 4 weeks (14·7 per cent ± 4·4 per cent *versus* 25·3 per cent ± 12·8 per cent, $P<0{\cdot}05$). Thus prazosin caused a major reduction in the development of neointimal hyperplasia which, together with reducing hypercontractility in these vessels[2], may give it a dual role in vascular surgery.

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Red cells contain a vasoconstrictor factor

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Transmission of infections such as AIDS and hepatitis has increased the need for a safer alternative to donor blood. Recent work has shown that a chemically modified haemoglobin solution, polymerized pyridoxylated haemoglobin (PPSFH) may fulfil this role[1]. Haemodynamic studies showed that this solution might have a vasoconstrictor effect[2]. PPSFH was prepared from outdated human red cells by a crystallization method (PPSFH(DV)) and by a chloroform extraction method (PPSFH(C)). Unmodified stroma-free haemoglobin was prepared by chloroform extraction from fresh pure red cells (SFA(PR)). A bioassay based on that of de la Lande[3] was used. An isolated rabbit ear artery was perfused with Krebs buffer. Viability and sensitivity were estimated by bolus injection of 60 pmol noradrenaline (Nor). The haemoglobin solutions were tested by using them as a perfusate, pressure rise is reported in mmHg.

Solution	Number of batches	Mean assay sensitivity (mmHg/60 Nor)	Pressure rise (mmHg)	
			Range	Mean
PPSFH(C)	11	18·3	7–55	24·5
PPSFH(DV)	7	26·2	0–7	2·[illegible]
SFH(PR)	4	14·75	21–68	32·5

These data show that haemoglobin solutions have a vasoconstrictor effect, which is significantly reduced ($P=0{\cdot}004$) when the crystallization method is used. This method employs long periods of static dialysis. We conclude that haemoglobin solutions contain a vasoconstrictor factor which is of low molecular weight and originates from red blood cells. The presence of such a factor has considerable implications for haemoglobin solutions as blood substitutes.

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Objective evaluation of stress tests with non-invasive (Duplex) measurement of volume flow

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Treadmill stress testing may not be applicable for follow-up of all femoropopliteal bypass grafts Supine exercise or postocclusive reactive hyperaemia (PORH) can be used. Quantification of changes in flow imposed by different tests is possible with Duplex scanning

In vitro validation from 422 paired observations demonstrated good correlation between timed fluid collection and Duplex measurement of volume flow (slope 1·07; intercept −5 ml/min; $R^2=93$ per cent).

Seven patients (six male; median age 70 years) with femoropopliteal bypass grafts were studied on two occasions 24 h apart. Resting flow (mean 167±27 s.e.m. ml/min) did not differ significantly between visits (paired *t* test; $t=0{\cdot}19$; $P=0{\cdot}86$). Flow was measured after 2 min exercise and PORH.

	Flow (ml/min) after.		
	0 min	2 min	5 min
Exercise	384	270	235
PORH	343	193	165

Flow was significantly higher after exercise at 2 and 5 min (paired *t* test, $t=2{\cdot}77$; $P=0{\cdot}016$ and $t=4{\cdot}3$; $P=0{\cdot}0009$) PORH tended to be difficult to reproduce within 2 min (paired *t* test; $t=2{\cdot}32$, $P=0{\cdot}059$) whereas exercise tended to be reproducible ($r=-0{\cdot}95$; $P=0{\cdot}38$).

Non-invasive measurement of volume flow permits characterization of the effect of different stress tests, quantification of changes in flow and objective assessment of reproducibility

Haemodynamic changes in the lower limb in claudicants after calcium antagonists

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Calcium antagonists exert a strong peripheral arterial vasodilatory effect but their role in atheromatous disease of the lower limb is undetermined.

In a double-blind cross-over manner, we studied the acute blood flow effects of nifedipine (20 mg sublingually) and nisoldipine (10 mg orally) in two groups of claudicants. Ankle/brachial Doppler systolic pressure index, common femoral artery volume blood flow (Duplex ultrasound) and pulsatility index were calculated.

Resting femoral blood flow increased by 55 per cent in response to nifedipine and 40 per cent after nisoldipine at 15 and 60 min respectively (pre-nifedipine$=269\pm31$ ml min^{-1}, increasing to 413 ± 47 ml min^{-1}, $P<0{\cdot}01$, $n_1=19$, pre-nisoldipine$=462\pm192$ ml min^{-1} increasing to 654 ± 303 ml min^{-1}, $P<0{\cdot}01$, $n_2=9$. The nisoldipine effect was prolonged with a 23 per cent increase recordable at 120 min. Ankle/brachial pressure index did not change significantly. Pulsatility index (a reflection of the peripheral resistance) had decreased significantly 60 min after nisoldipine (pre-dose$=5{\cdot}6\pm1{\cdot}3$; post-dose$=4{\cdot}4\pm1{\cdot}3$; $P<0{\cdot}04$). Placebo did not influence limb blood flow

We conclude that both nifedipine and nisoldipine significantly increase lower limb blood flow in claudicants, without reduction of ankle/brachial pressure index. This group of agents should prove useful in the medical management of patients with peripheral vascular disease

Duplex scan velocity measurements in the detection and grading of vein graft stenoses

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The aim of this study was to determine whether Duplex scanning of femorodistal vein grafts could reliably detect and grade graft stenoses.

One hundred and six grafts were studied 6–12 months postoperatively with Duplex scanning to measure peak velocities proximal (V_1) and at a point (V_2). Without knowledge of the result, intravenous digital subtraction angiography (IV DSA) was then obtained in all patients and reported independently. Twenty-four of the grafts were studied by two independent observers with Duplex scanning to determine measurement errors. The coefficient of experimental error for flow was 31 per cent and for peak velocity 15 per cent.

The ratio $V_2{:}V_1$ was used to detect and grade stenoses and the results were compared with angiographic findings·

Angiographic stenosis	$V_2{:}V_1$
Nil ($n=83$)	1·0–1·5
Mild <33% ($n=12$)	1·8–2·4
Moderate 33–66% ($n=6$)	2·3–3·9
Severe >66% ($n=5$)	5·5–6·3

The Duplex-measured $V_2{:}V_1$ ratio identified all 23 stenoses and correctly graded 22 (96 per cent) of these. Only the five severe stenoses were symptomatic and these were successfully repaired before graft failure. These data indicate that velocity changes, even in relation to minor asymptomatic stenoses, are large when compared with measurement errors. The $V_2{:}V_1$ ratio can detect graft stenoses (i.e. >1·5) and can be used to grade the severity of the lesion As a consequence of the ability to detect all stenoses and thus to correct severe lesions prophylactically before graft occlusion occurs, we believe that Duplex scanning is the most essential non-invasive method for the follow-up of patients with femorodistal grafts.

Do arteriogram scores predict outcome after femorodistal bypass?

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The suitability of patients for femorodistal bypass is usually based upon the pre-operative arteriogram. Various scoring systems have been used in an attempt to predict peripheral resistance and outcome.

We have reviewed the arteriograms in 41 consecutive patients undergoing femorodistal bypass grafts. Three well-established scoring systems (A, B and C) were compared with the pre-operative pulse-generated runoff score (PGR), the pre-operative measurement of distal resistance (DR) and the post-papaverine graft resistance (PPGR)

There was a significant correlation between the PGR score and the DR ($r_s=-0{\cdot}61$, $P<0{\cdot}001$). No correlation was found between the arteriogram scores A, B or C and DR. There was no significant difference between the arteriogram scores A, B and C for successful and failed grafts at 1 month The PGR score, DR and PPGR for successful grafts were significantly better than those for grafts that failed at 1 month (Mann–Whitney *U* test, $P<0{\cdot}0015$, $P<0{\cdot}0001$, $P<0{\cdot}0008$, respectively).

These results suggest that arteriogram scoring systems are unable to predict either peripheral resistance or outcome after femorodistal bypass. Selection for surgery should be based upon a combination of PGR data and arteriography and not on arteriography alone.

In situ vein femorodistal bypass: does vein size matter?

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Of 85 *in situ* vein femorodistal bypass grafts, 31 were performed for rest pain and 54 for tissue loss A total of 23 patients were diabetic, 41 had coexisting coronary or cerebrovascular disease and 44 were still smoking.

In all, 91 limbs were explored and only 6 long saphenous veins were rejected because they were incomplete or had a minimum internal diameter of <2 mm (median 4 mm, range 2–8 mm). The vein was fully mobilized via a groin-to-knee incision, ligating all the tributaries. This ensured a tension-free proximal anastomosis to the common femoral artery and removed the risk of subsequent A–V fistulae The distal anastomosis was to the infrageniculate popliteal in 47, the tibioperoneal trunk in 19 and a single crural vessel in 17 cases; distal arteriographic runoff was by three vessels in 16, two in 33 and one in 36 cases.

Results were analysed by the Life Table method with a minimum follow-up period of 6 months. The primary failure rate at 1 month was 22 per cent and the secondary failure rate (following revision) was 12 per cent. The cumulative patency rate at 1 and 2 years was 77 per cent and 72 per cent, limb salvage 85 per cent and 77 per cent and patient survival 89 per cent and 83 per cent, respectively. The only significant risk factors were the level of the distal anastomosis and the runoff ($P = 0{\cdot}002$ and $0{\cdot}003$).

Our 2-year patency rate is comparable with most other reported series. The disadvantage of interrupting the vasa vasorum by complete mobilization appears to be a theoretical risk only. A high utilization rate of >90 per cent can be obtained if small-calibre veins are used. The diameter of the vein appears not to affect the 2-year patency rates even when using veins of 2 mm.

Changes in hepatic haemodynamics in rats with overt liver tumour

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We have previously reported the changes in hepatic haemodynamics during the early growth and development of hepatic micrometastases in the rat[1]. In the present study, we describe the alterations in the hepatic perfusion index (HPI) and liver blood flow in the presence of overt hepatic tumour

Three weeks after an intraportal injection of $1{\cdot}6 \times 10^{7}$ Walker carcinosarcoma cells in male Fisher rats, overt tumour was evident in the liver. A control group received an intraportal injection of isotonic saline. The HPI was measured by dynamic scintigraphy and hepatic haemodynamics by a radiolabelled microsphere technique. Intrahepatic arteriovenous shunting was determined after an hepatic artery injection of ^{99m}Tc-labelled macroaggregated albumin (20 μm)

The HPI in rats with overt tumour ($0{\cdot}61 \pm 0{\cdot}99$; $n = 10$) was significantly higher ($P < 0{\cdot}001$, Student's *t* test) than in control rats ($0{\cdot}32 \pm 0{\cdot}7$, $n = 10$). Arterial flow to tumour was significantly greater than to normal liver tissue in both tumour-bearing and control rats ($1{:}1{\cdot}19 \pm 0{\cdot}18$; $P < 0{\cdot}05$). Intrahepatic shunting was also significantly increased ($P < 0{\cdot}001$) in rats with tumours compared with controls. Extrahepatic artery blood flow did not alter, but portal venous inflow was reduced in rats with liver tumour.

These results confirm observations in man that the HPI alters when overt metastases are present in the liver and that blood flow to these tumours is principally arterial[2]. Although the hepatic arterial flow did not change, the increase in shunts suggests that intrahepatic arterial blood is diverted to the tumour, possibly via intrahepatic shunts.

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2. Leveson SH, Wiggins PA, Giles GR, Parkin A, Robinson PJ Deranged liver blood flow patterns in the detection of liver metastases. *Br J Surg* 1985; **72**: 128–30

Relationship between dynamic liver scintigraphy and percentage hepatic replacement with liver metastases

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By dynamic liver scintigraphy an index of the mesenteric fraction (MF) of hepatic blood supply can be calculated. This index is reduced significantly in tumour regions of interest (ROI) compared with normal liver regions.

Fasting dynamic liver scintigraphy was performed in 45 patients with colorectal liver metastases and 21 controls, and the MF determined for the maximal tumour and liver ROI. Patients were investigated by standard static isotope scan (43), ultrasound scan (43), and CT scan (34). A specialist in each modality estimated the percentage hepatic replacement with tumour (PHR): stage 1, <25 per cent; stage 2, 25–50 per cent; stage 3, >50 per cent. Operative assessment of PHR was also made when possible (26).

MF from the maximal ROI was significantly lower in metastatic livers than in controls ($0{\cdot}51 \pm 0{\cdot}03$ s.e.m. *versus* $0{\cdot}68 \pm 0{\cdot}02$; $P = 0{\cdot}0001$) The MF showed a significant negative correlation with overall PHR ($P < 0{\cdot}01$). When analysed separately, static isotope scan ($P < 0{\cdot}001$) and CT scan ($P < 0{\cdot}02$) displayed a significant relationship between PHR estimates and MF. The arterial component of effective hepatic reticuloendothelial flow (K_{art}) showed a significant increase with PHR ($P < 0{\cdot}025$)

Our results show a correlation between the PHR and MF. There is evidence suggesting an absolute increase in total hepatic arterial blood flow. Static isotope and CT scan assessment of PHR correlate with the MF.

1 Fleming JS, Ackery DM, Walmsley BH *et al.* Scintigraphic estimation of arterial and portal blood supplies to the liver. *J Nucl Med* 1983, **24**: 1108–13.
2. Flowerdew ADS, McLaren MI, Fleming JS *et al.* Liver tumour blood flow and responses to arterial embolization measured by dynamic hepatic scintigraphy. *Br J Cancer* 1987; **55**: 269–73.

Prognostic value of DNA aneuploidy in papillary thyroid cancer—a comparison of static densitometry and flow cytometry

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DNA aneuploidy may be an independent prognostic factor in malignancy. The evidence in various tumours is conflicting but in papillary thyroid carcinoma DNA aneuploidy has been found to be a highly significant prognostic factor[1].

The prognostic accuracy of flow cytometric and static densitometric DNA analysis was compared in 34 patients who had undergone surgery for papillary thyroid cancer between 1959 and 1978 (median follow-up 18 years). Static densitometry was performed on thin paraffin sections and flow cytometry on disaggregated thick paraffin sections: technically satisfactory preparations were made in 31 cases.

Five patients died of thyroid cancer Three of six patients found to have DNA aneuploid tumours by flow cytometry died of thyroid cancer ($P > 0{\cdot}05$, Fisher's exact test) compared with four of eight patients found to be aneuploid by static densitometry ($P < 0{\cdot}02$) In contrast, quantitative static densitometry correctly identified all five patients dying of cancer, with no false positives ($P < 0{\cdot}002$).

The presence of non-tumour cells is a limiting factor in the accuracy of flow cytometric measurement of the percentage of DNA aneuploid tumour nuclei and is less accurate than static densitometry, in which morphological selection of malignant cells permits quantitative measurements increasing the prognostic accuracy.

1 Cohn K, Backdahl M, Forsslund G *et al* Prognostic value of nuclear DNA content in papillary thyroid carcinoma. *World J Surg* 1984, **8**. 474–80.

Selective destruction of experimental colon cancer using photodynamic therapy

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Photodynamic therapy (PDT) involves the administration of a photosensitizing agent which is selectivity retained in malignant tissue Activation of the sensitizer with light produces a cytotoxic species that results in local tumour destruction We have investigated aluminium sulphonated phthalocyanine (AlSPc) as an agent for destruction of dimethyl hydrazine (DMH)-induced colonic cancer in Wistar rats. AlSPc concentration was measured by fluorescence emission after alkali extraction at a range of times after intravenous injection of 5 mg kg^{-1}. It was selectively retained in DMH tumours 24–48 h after IV injection, with a tumour·normal ratio of 2:1. An argon pumped-dye laser tuned to 675 nm coupled to a flexible 0·2 mm optical fibre was used to irradiate the tumours and normal colon ($n = 45$) at laparotomy and the animals allowed to recover The amount of necrosis was measured 72 h after treatment. Using a photosensitizer dose of 5 mg kg^{-1} there was no difference between the damage in normal and malignant tissue with ($5{\cdot}5 \pm 0{\cdot}6$ mm) necrosis. However, by using one-tenth of the dose (0·5 mg kg^{-1}) up to 2 mm of damage could be produced in tumour with no damage to normal colon Fluorescence measurement of AlSPc in treated areas showed that it was photodegraded before a threshold PDT dose was reached in normal tissue, the tumours containing more AlSPc reached PDT threshold and were destroyed. Selective destruction of colonic cancer is possible using photodynamic therapy

Handling of the bowel during surgery promotes tumour formation in an experimental model

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Many factors may lead to tumour 'recurrence' after colonic resections. The role of handling was investigated in 104 Fischer-344 rats randomized into five groups At 10 weeks of age, groups 2–5 had 10 weekly subcutaneous injections of azoxymethane at a dose of 7 mg/kg body weight. Group 1 acted as controls. At week 21 all groups had a laparotomy Anastomoses were created at 9 cm from the anus in groups 1 and 2. In group 3 the distal colon was handled by gentle massage between finger and thumb Groups 4 and 5 were analysed separately, group 4 was handled proximally and group 5 was handled in the same manner as group 3. At week 37, the animals were killed and the tumours were classified histologically. The tumours were documented as having occurred in the proximal colon (from caecum to 10 cm from anus), the distal colon (within 10 cm of the anus) or in the caecum.

There was an increased tumour yield at the site of the anastomosis (group 2) compared with the remainder of the bowel ($P<0\cdot001$) In group 3 there were also more tumours present in the handled distal bowel ($P<0\cdot01$), compared with the proximal bowel or caecum. Groups 4 and 5 also showed tumours predominating in the handled bowel, whether proximal (group 4, $P<0\cdot01$) or distal (group 5, $P<0\cdot05$)

Handling of the bowel alone resulted in increased tumours, suggesting its importance in tumour 'recurrence'

Stearic acid and carcinogenesis

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Malignant transformation of the cell is accompanied by a decrease in membrane rigidity, resulting in part from the desaturation of stearic acid to oleic acid. The aim of this study was to investigate the influence of stearic acid on tumour development *in vivo*.

Nitrosomethylurea (NMU) rapidly induces mammary carcinomas in rats. Administration was by IV injection via the tail vein at a dose of 5 mg/100 g body weight. Two groups of female Sprague-Dawley rats received either NMU ($n=20$) or NMU plus iodostearic acid ($n=23$) Gas–liquid chromatography was used to study changes in the fatty acid composition of rat erythrocyte membranes during mammary carcinogenesis

By week 16, 19 of 20 rats in the NMU group and 8 of 19 rats in the NMU plus iodostearic acid group developed tumours. The mean number of tumours/rat was 3·8 in the NMU group and 2·7 in the NMU plus iodostearic acid group The mean saturation index (ratio of stearic acid to oleic acid) of rat erythrocytes was 2·0±0·3 in rats receiving normal saline and 1·09±0·28 in the NMU group ($P<0\cdot001$).

These data indicate that iodostearic acid inhibits tumour development in rats. In addition, the onset of tumours is associated with a fall in the saturation index of rat erythrocytes.

Melanoma growth in vivo is inhibited by dietary intake of primrose oil and fish oil

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Little is known about dietary or metabolic effects in the pathogenesis of malignant melanoma. Mouse melanoma cell growth has been inhibited by addition of γ-linolenic acid *in vitro*[1], which was explained as a metabolic block in the utilization of essential fatty acids.

Athymic nude mice were inoculated subcutaneously with 2×10^6 human melanoma G361 cells. Groups of 12 mice were fed either a normal control diet or diets supplemented with 5 per cent (w/w) evening primrose oil or 5 per cent fish oil beginning 1 week before inoculation. Tumours were removed and examined histologically after 5 weeks.

Tumour number and weight were significantly reduced in mice fed evening primrose oil (Mann–Whitney $U=31$, $P=0\cdot02$) and fish oil (Mann–Whitney $U=37$, $P=0\cdot05$) This was partly due to diminished take of melanomas (see *Table*) and also smaller tumour weights in the treated groups.

	Control	5% EPO	5% Fish oil
Tumour take/total injected	9/12	4/12	5/12
Tumour weight (mg) mean ± s.e.m.	340±101	111±82	160±71

Dietary modification using fatty acids may have a role in therapy of malignant melanoma.

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Effect of photodynamic therapy on normal and tumour microcirculation in the rat

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In photodynamic therapy (PDT), systemically administered photosensitizing drugs such as dihaematoporphyrin ether (DHE) are reported to localize in tumours. Light activation then results in tumour necrosis with limited damage to normal tissues As tumour necrosis may be partly due to reduced blood flow, we compared the effect of PDT on the vasculature of the normal rat cremaster muscle and of an implanted sarcoma in the cremaster. Forty-eight hours after DHE injection (10 mg/kg IP) the cremaster, with blood supply from the rat intact, was positioned in a tissue bath and the vasculature was observed by *in vivo* microscopy DHE was activated by light (530–560 nm) from a mercury arc lamp (120 J/cm²). Data (mean ± s.e.m.) show vessel red cell column diameter (RCCD) in tumour and normal arterioles and venules, and stasis of blood flow (percentage of vessels without flow after PDT).

	Initial RCCD (μm)	Minimum RCCD (μm)	Stasis (%)
Artery (tumour)	42±5	11±4*	90%
Artery (normal)	45±4	10±2*	90%
Vein (tumour)	44±5	17±3*	75%
Vein (normal)	44±5	22±4*	85%

* $P<0\cdot05$ (paired t test, $n=8$)

Exposure to drug or light alone had no effect, but together they caused significant narrowing of RCCD and decreased blood flow in normal and tumour vessels. As responses were similar, there is no evidence in this model for a selective effect of PDT on tumour vessels compared with normal vessels.

Gastric mucosal haemodynamics and susceptibility to injury in portal hypertension

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The propensity of the gastric mucosa to ulcerate in portal hypertension remains controversial. This study examines level of mucosal perfusion and susceptibility to injury in two rat models of portal hypertension.

Pre-hepatic portal hypertension was produced using the portal vein ligation technique. There was no significant difference in sodium taurocholate-induced (40 mM; 1 ml $100\,g^{-1}$) injuries in 7-day portal vein-ligated animals compared with sham-operated controls (16·4±7·9 $n=13$ *versus* 16·5±5·5 mm², $n=13$; mean ± s.e.m.). Gastric mucosal blood flow was measured in separate animals using an autoradiographic technique[1] There was no significant difference in mucosal perfusion between ligated and control animals (208·8±31, $n=7$ *versus* 176·3±9·9 ml $100\,g^{-1}\,min^{-1}$, $n=6$).

Severe decompensated cirrhosis with ascites, elevated portal pressure and hypoalbuminaemia was produced after 10 weeks gavage with carbon tetrachloride There was no significant difference in either lesion score (26·3±6·3, $n=12$ *versus* 52·5±14·5 mm², $n=15$) or gastric mucosal blood flow (214 ± 38·5, $n=6$ *versus* 165·8 ± 17·3 ml $100\,g^{-1}\,min^{-1}$, $n=6$) between cirrhotic and control groups.

Both portal hypertensive models, demonstrating no significant difference in level of mucosal perfusion or mucosal susceptibility to injury compared with controls, suggest that the portally hypertensive gastric mucosa is not more vulnerable to erosion formation.

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What are the nutritional consequences of total gastrectomy?

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Total gastrectomy (TG) with Roux-en-Y reconstruction (RY) provides a barrier to bile reflux but results in substantial weight loss. The nutritional consequences of TG with RY were investigated in 12 male patients (age 24–84 years), 2–15 years after resection. Weights were stable, and there was no evidence of recurrent disease. Dietary intake was calculated using a diary method. Resting energy expenditure (REE) was measured by indirect calorimetry and body composition by *in vivo* neutron activation analysis, dilution of ^3H_2O and anthropometric techniques. Body composition was compared with predicted values for individuals of the same gender, age and height. Function of adductor pollicis was measured using a strain gauge technique[1]

All patients were Visick I or II. Mean dietary intake was 3300 kcal/day—more than twice the mean REE of 1350 kcal/day.

	Weight (kg)	Body protein (kg)	Body fat (kg)	Body water (kg)	Muscle function force frequency (%)
Patients ($n=12$)	57	9	7	39	40
Predicted normal	73	12	18	43	35
Deficiency (%)	22	25	61	9	—
$P<$*	0·01	0·05	0·01	0·05	0·05

Data are medians; * Mann–Whitney U test

After TG with RY calorie intake was high, but weight, body fat and lean body mass were significantly less than normal. As REE remained normal, weight loss was probably due to reduced efficiency of digestion and absorption, and not to reduced food intake.

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Feeding produces positive nitrogen balance by decreasing the breakdown component of whole-body turnover

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The effect of feeding on whole-body protein turnover in man, measured by infusing trace amounts of labelled amino acid, is uncertain Feeding has been shown to cause either no change or a large increase in protein synthesis[1]. We studied five volunteers who were fed hourly meals for 12 h and then fasted for 12 h on each of three occasions (A–C), varying only the duration of (L-[1-^{13}C]) leucine infusion. When leucine was infused for the entire 24 h (A), feeding appeared to increase both synthesis and oxidation and to decrease breakdown, compared with fasting ($P<0·005$) When leucine was infused for the last 4 h only of each nutritional period, there was no significant change in protein synthesis on feeding, while breakdown fell dramatically ($P<0·001$) Moreover, with cessation of infusion after 12 h of feeding (C), label was still detectable 10–12 h later in both breath and plasma Tracer recycling, therefore, occurs even after 12 h infusions.

We conclude that protein turnover is best studied by infusing tracer for the minimum period, consistent with attainment of isotopic plateau, in order to minimize the problem of recycling of label. Our results suggest that mixed feeding induces positive nitrogen balance by decreasing breakdown, leaving synthesis unaffected.

1. Reeds PJ, Garlick PJ. Nutrition and protein turnover in man In Draper HH, ed. *Advances in Nutritional Research 1984; Vol 6*. New York: Plenum Press, 1984: 93–138.

Respiratory function after injection sclerotherapy for oesophageal varices

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Acute respiratory failure, thought to result from blood cell microembolization, is a rare complication of injection sclerotherapy (IS) for oesophageal varices However, the incidence of pulmonary dysfunction after IS in asymptomatic patients is unknown. Therefore, this study was undertaken to determine the effects of IS on respiratory function in patients without overt pulmonary complications.

Vital capacity (VC) and blood gases were measured pre- and postoperatively in 11 patients undergoing IS with ethanolamine oleate on 15 occasions under general anaesthesia. A control group comprised five patients who underwent oesophagogastroscopy on six occasions, but did not receive IS. On a further 14 occasions, blood platelet and leucocyte concentrations were measured before and 5 and 60 min after IS. The same measurements were carried out on a control group who underwent oesophagogastroscopy but were not injected

IS resulted in a decrease in both VC(0·27 litres) and P_{aO_2} (6·2 ± 2·8 mmHg). In controls VC was not altered but P_{aO_2} increased (3·4 ± 1.9 mmHg). There was a significant positive correlation between the changes in P_{aO_2} and VC ($r=0·787$, $P<0·001$) in patients who received IS. Leucocyte and platelet concentrations did not change in either group of patients.

These results suggest that IS is associated with a deterioration in respiratory function which may be secondary to increased pulmonary compliance resulting from sclerosant embolizing to the lung, but is unrelated to alterations in blood leucocyte or platelet concentrations.

Renal nerves in mineralocorticoid-induced hypertension

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Adrenalectomy may fail to relieve hypertension in up to 50 per cent of patients with Conn's syndrome. This 'resistant' hypertension may result from resetting of renal mechanisms controlling arterial pressure. Using a rat model of mineralocorticoid-induced hypertension we have shown that such resistant hypertension is reversed for only 3–4 weeks after transplantation of a normal kidney to hypertension recipients[1]

In order to determine whether the recurrence of hypertension post-transplant is a result of graft sympathetic reinnervation, and thereby sodium retention, the pattern of nerve regeneration and exchangeable body sodium was examined after renal transplantation. Indirect immunofluorescence to a range of neuropeptides revealed nerve regrowth beyond the arterial anastomosis by 4 weeks, but renal parenchymal innervation was not apparent until 10 weeks post-transplant. Similarly, indirect evidence of innervation obtained using a radioenzyme assay of noradrenaline from grafts examined at weekly intervals post-transplant revealed levels within the denervation range (0–26 ng/g of controls, range 110–289 ng/g) up to 8 weeks post-transplant. Exchangeable body sodium rose significantly ($P<0·05$) from 34·6 ± 1·3 mmol/kg before transplantation ($n=6$) to 44·7 ± 1·8 mmol/kg (1 week post-transplant) and remained elevated, 37·3 ± 1·5 mmol/kg ($P<0·05$) (10 weeks post-transplant), with no relationship to the pattern of denervation and reinnervation.

These findings suggest that, although reinnervation occurs, the recurrence of hypertension in this model cannot be explained by an effect of the renal nerves.

1 McMillan I, Bolton EM, Bradley JA, Lever AF, Brown WB. Demonstration of an extra-renal mechanism in post deoxycorticosterone- hypertension *Transplant Proc* 1987; **19** 1113–4

Do we need to wear face masks in theatre?

D.E. Beverland, K.B. Bamford, R. Gilliland, J.S.G. Murphy, T.G. Parks and C.C. Patterson, *Queen's University of Belfast, Belfast, UK*

This paper presents the results of a prospective controlled trial involving approximately 7000 patients in four Belfast hospitals during a 2½ year period. Its purpose was to assess the efficacy of face masks in the prevention of wound infection. The data were managed using an IBM computer.

On alternative weeks face masks were not worn by theatre staff. Operative details were completed on a trial form in theatre without disclosing whether masks were worn. Subsequent details were completed in the ward with a wound infection being defined as discharge of pus Any missing details on each form were added by the first author before its removal from the ward. If a patient was discharged before suture removal then the wound was checked either by district nurse or from the notes after the 6-week review. The incidence of infection for different operative categories in those analysed to date is as shown in the *Table*.

	With masks		Without masks		With and without masks	
Operative category*	Total	With infection†	Total	With infection	Total	With infection
1	1916	57 (3·0)	1870	66 (3·5)	3786	123 (3·2)
2	816	33 (4·)	855	38 (4·4)	1671	71 (4 2)
3	665	54 (8·1)	682	46 (6·7)	1347	100 (7·4)
1+2+3	3397	144 (4·2)	3407	150 (4·4)	6804	294 (4·3)

* Categories: 1, clean; 2, potentially contaminated; 3, contaminated
† Percentages in parentheses

In conclusion, in this trial face masks did not significantly affect the overall incidence of wound infection.

Effect of transdermal glyceryl trinitrate on the survival of peripheral intravenous infusions

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The aim of this prospective double-blind controlled study was to test the hypothesis that infusion phlebitis is initiated by venoconstriction at the infusion site, hence treatment with a vasodilator may reduce its incidence. Three hundred and forty patients were randomized to receive, immediately after venous cannulation and distal to the infusion site, a self-adhesive patch of transdermal glyceryl trinitrate (Transiderm-Nitro 5®) or identical placebo. Infusions were discontinued when they were no longer required for treatment or when they failed. Failure incidence was analysed by life-table method and log rank test.

Of the infusions, 55 per cent (94 out of 170) failed in the control group compared with 19 per cent (33 out of 170) in the treatment group ($\chi^2 = 46$, $P < 0{\cdot}0005$). The commonest cause of infusion failure was superficial phlebitis; 47 per cent in the control group and 17 per cent in the treatment group ($\chi^2 = 34$, $P < 0{\cdot}0005$). The estimated median time of infusion survival was 74 h in the control group compared with 127 h in the treatment group (log rank $\chi^2 = 143$, $P < 0{\cdot}0001$). Differences in infusion survival between control and treatment groups remained significant when allowance was made for differences between males and females, cannulae size and site, and drug additives using a proportional hazards model ($Z = 10{\cdot}4$, $P < 0{\cdot}001$, relative risk of failure in the treatment group = 0·09, 95 per cent CI 0·06–0·15).

We conclude that superficial phlebitis is a pervasive problem and its incidence can be reduced effectively by transdermal glyceryl trinitrate

Calcium alginate haemostatic swabs in general surgery: a randomized clinical trial

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Haemostasis is essential in all surgery with ligature and diathermy to control bleeding vessels and gauze swabs to control oozing and absorb blood. Calcium alginate (Kaltostat), which can be economically made into absorbent swabs, controls experimental haemorrhage very much more rapidly than oxidized cellulose (Surgicel) or collagen (Medistat) and is absorbable[1]

Fifty-nine operations performed by surgeons with FRCS were randomized to surgical gauze or calcium alginate swabs which were applied to all cut surfaces after vessel control by diathermy or ligature. All blood lost was collected, haemolysed with potassium cyanide, and haemoglobin concentration compared with a pre-operative venous sample by haemoglobinometer.

	Blood loss (ml)		
	Cholecystectomy ($n = 19$)	Mastectomy ($n = 18$)	Hernia ($n = 22$)
Gauze ($n = 31$)	147 ± 20	221 ± 17·5	21·3 ± 8
Calcium alginate ($n = 28$)	96 ± 8·4*	142 ± 12·2**	19 6 ± 3

All results are mean ± s.e.m.
* $P < 0{\cdot}05$, ** $P < 0{\cdot}01$, Mann–Whitney *U* test

Overall blood loss was considerably reduced from a mean of 132·6 ± 17·6 ml for gauze to 75 ± 10 7 ml for calcium alginate ($P < 0{\cdot}01$). This difference was most significant for mastectomy ($P < 0{\cdot}01$). Mean operation times for all procedures were also reduced from 49·4 ± 3 min with gauze to 34·9 ± 2 5 min ($P < 0{\cdot}01$) This saving in operation time was again most marked for mastectomy at 40 ± 3·5 compared with 51 ± 4 9 min ($P < 0{\cdot}02$) but was also significant in cholecystectomy.

Calcium alginate swabs reduce operative blood loss and consequently save time. If this material can be mass produced economically it may replace gauze in surgery involving substantial oozing from cut surfaces.

1. Blair SD, Backhouse CM, Matthews J, McCollum CN. Haemostatic agents in experimental liver wounds. *Br J Surg* 1986; 73: 1025–6.

Abnormal gastric adaptive relaxation in patients with gastro-oesophageal reflux

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Gastric adaptive relaxation may have a role in the pathophysiology of gastro-oesophageal reflux (GOR). We measured gastric adaptive relaxation in 15 normal healthy volunteers (control) and in 12 patients with symptomatic GOR confirmed by 24 h pH monitoring. Controls were: 13 men, 2 women; median age 30 years, range 22–41 years; median body weight 70 kg, range 50–79 kg All were asymptomatic on no medication. The GOR group were: 8 men, 4 women; median age 48 years, range 23–65 years, median body weight 77 kg, range 60–92 kg. Endoscopy showed. no abnormality, five patients; hiatus hernia with oesophagitis, four patients; oesophagitis only, three patients. Medication was withheld for 12 h before study

Fasted subjects were intubated with a Ryle's tube containing a pressure microtransducer within a flaccid plastic bag (800 ml). Gastric corpus–fundus pressure was recorded during distension of the bag with 460 ± 20 ml (mean ± s.d.) air over 30 s. Pressure indices (median· range) derived from areas under the pressure curves were. control, 12·7 (7·5–17·1) cmH_2O, GOR, 9 1 (6·4 ± 13·3) cmH_2O, $P < 0\ 01$ (Mann–Whitney *U* test). No correlation was found between pressure indices and age, sex or body weight

The results confirm that corpus–fundus motility is abnormal in patients with GOR. This novel finding may explain the delayed gastric emptying found in some patients[1].

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Effect of simulated intraduodenal haemorrhage on gastric acid secretion, gastric motility and gastrointestinal (GI) hormones

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The majority of acute upper GI bleeds stop spontaneously despite the adverse local environment, suggesting the existence of locally protective mechanisms to facilitate haemostasis. We have investigated the effects of simulated intraduodenal haemorrhage on acid secretion, gastric emptying and GI hormones.

In seven healthy volunteers, the effect of intraduodenal (ID) infusion of 160 ml autologous venous blood and 160 ml egg-white (similar CHO and protein content to blood) on submaximal pentagastrin-stimulated gastric acid secretion was examined. GI hormone response was also studied. In a further six subjects the effect of ID blood infusion on gastric emptying was studied in randomized fashion using a double-sampling test meal technique.

ID blood infusion reduced acid output (mmol/h) from 29·9±3 to 21·4±3·7 (mean±s.e.m., $P<0{\cdot}02$). In contrast ID egg-white increased acid output from 31·8±2·8 to 33·0±4·4 (n.s.). Mean plasma GIP increased by 69 per cent after ID blood infusion ($P<0{\cdot}02$) but did not change after egg-white infusion. ID blood resulted in a significant delay in gastric emptying at 30, 40 and 50 min post-infusion ($P<0{\cdot}02$).

In conclusion, this study has demonstrated that simulated ID haemorrhage (1) reduces gastric acid secretion, (2) inhibits gastric emptying, and (3) increases plasma GIP. These effects may be important in providing a more favourable environment for haemostasis to occur

FED patterns of gastrointestinal (GI) activity detected by surface vibration analysis (SVA): influence of viscus

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Distinct FED-phase patterns of GI activity are detected by SVA after a standard solid meal in normal volunteers. SVA, however, is a non-invasive test which captures energy from the entire GI tract and the individual contribution of gastric, small bowel or colonic contractions to the overall signal is unknown. To address this question, this study has evaluated GI activity by SVA for 30 min fasting and 180 min in the FED phase, after a standard solid meal in 6 patients after a total gastrectomy, 10 patients after a total colectomy, and 28 normal volunteers. Oral-to-caecal transit times were also measured in gastrectomy patients and in volunteers.

Results	Fasting	Fed (min)					
SVA values		30	45	60	75	135	180
Normals	12·9	20·8	16·2	14·6	13·5	16·1	18·6
Pulsed gastrectomy	11·6	43·3	37·2	25·7	39·2	21·8	18·9
*P**	n.s.	<0·05	<0·05	<0·05	<0·01	<0·05	n.s.
Pulsed colectomy	14.8	30·2	20·1	13·5	13·1	13·1	15·3
*P**	n.s.	n.s.	n.s.	n.s.	n.s.	n.s	n s

* Patient values *versus* normals by Mann–Whitney *U* test

Oral-to-caecal transit times were more rapid in gastrectomy patients than in normals (mean±s.e.m. = 75+16 *versus* 231±15·5 min $P<0{\cdot}01$).

In conclusion, the FED response shown by SVA is similar in colectomy patients and controls, which suggests little early colonic contribution. The significantly greater response in gastrectomy patients underlines the 'regulator' role of the intact stomach which acts as a 'brake' to small bowel activity.

Role of cholinergic pathways, cholecystokinin and gastrin in the gastric phase of gallbladder emptying in man

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Balloon distension of the stomach initiates gallbladder emptying (GBE) in man[1]. To investigate whether the gastric phase of GBE is mediated by cholinergic pathways, the effect of truncal vagotomy and pyloroplasty (TVP) ($n=9$) and atropine ($n=7$) were studied and compared with a control group of healthy volunteers ($n=9$). ^{99}Tc^{m}-EHIDA cholescintigraphy was used as the biliary tracer and intragastric balloon distension as the stimulus. Changes in circulating cholecystokinin and gastrin levels were measured by bioassay and radioimmunoassay respectively.

In response to gastric distension GBE occurred in six control subjects, but in only four TVP subjects ($P=0{\cdot}6372$, n s Fisher's exact test). Gallbladder emptying did not occur in any of the subjects given atropine ($P=0{\cdot}0144$ cf. control group, $P=0{\cdot}088$, n.s. cf. TVP group, Fisher's exact test). Plasma cholecystokinin did not rise significantly from basal levels after gastric distension ($P>0{\cdot}5$, n.s Wilcoxon's sign rank test), although there was a small but significant rise in the serum gastrin levels ($P<0{\cdot}05$ Wilcoxon's sign rank test).

These results suggest that the gastric phase of GBE, which is inhibited by atropine but not by TVP, is initiated by a non-vagal cholinergic reflex. Cholecystokinin and gastrin are unlikely to have a major role in this putative gastrocholecystic reflex.

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Pre-operative risk factors in patients with common bile duct (CBD) stones—the presence of medical risk factors (MRF) should determine treatment policy

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Independent pre-operative risk factors in patients with CBD stones have not been previously determined either in surgical patients or in those undergoing endoscopic sphincterotomy (ES), thus confounding treatment options.

A multivariate analysis of 30 factors was performed in 325 patients undergoing surgery with or without pre-operative ES (Group A) and in 190 patients undergoing ES (Group B) Post-procedural complications occurred in 83 patients (26 per cent) in Group A and in 32 (17 per cent) in Group B. Univariate analysis revealed that age and serum urea, creatinine, albumin and bilirubin were all associated with increased complications in both groups ($P=0{\cdot}03$ to $P<0{\cdot}0001$). In Group A, however, only bilirubin, pre-operative ES and MRF were *independently* significant in predicting complications (logit $P=0{\cdot}51\,[\mathrm{MRF}]+0{\cdot}053\,[\mathrm{ES}]+0{\cdot}003\,[\mathrm{Bil}]-1{\cdot}63$; in Group B only bilirubin and albumin were *independently* significant but *not MRF* (logit $P=1{\cdot}46-0{\cdot}107\,[\mathrm{Alb}]+0{\cdot}004\,[\mathrm{Bil}]$).

The following conclusions can be drawn: (1) post-procedural risk is directly related to the level of bilirubin *irrespective* of the proposed treatment; (2) patients with MRF are potentially best treated by ES alone—without surgery, (3) patients without MRF should be treated by surgery *without* pre-operative ES.

T tubes: virgin, slit, guttered or sculpted?

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T tubes are commonly used after bile duct exploration, but surgeons vary in the modifications they make to the standard latex T tube. Biliary leakage and peritonitis may follow removal of the T tube[1] Such complications probably arise from duct or tract trauma

The mechanics of T tube removal have been studied *in vitro* using a standard 16G Kehr T tube either (1) unmodified (virgin), (2) with the ductal tube cut open (slit), (3) with half the ductal tube removed (guttered), or (4) guttered with a 'V' cut out opposite the stem of the tube (sculpted). Five tubes of each design were pulled through 10 rigid circular holes ranging from 16G to 30G in diameter. The junction of the T tube provided obstruction to removal of the tube and this was not affected by the length of the side arms. At all hole sizes, the forces required to remove the four designs of tube were significantly different from each other ($P<0{\cdot}05$, *t* test). Virgin tube: 16G hole = 20·5 N±2·4 (mean±s.e.m.) to 30G hole = 3·7±0·4; slit tube: 16G = 14·6±2·0 to 30G = 2·2±0·1; guttered tube: 16G = 6·6±0·6 to 30G = 0·7±0·1; sculpted tube: 16G = 1·8±0·3 to 30G = 0·3±0·1.

Modifications of the standard T tube resulted in reductions in the force required for 'removal' of up to 92 per cent, and such tubes are now being used clinically. These modifications should be important in preventing complications of T tube removal.

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Gallstone formation is associated with diminished gallbladder motility

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Cholestasis may lead to gallstones (GS). We investigated the relationship between gallbladder (GB) sensitivity to cholecystokinin (CCK) and GS formation

In experiment 1, 10 guinea pigs (GPs) were fed a normal diet (ND), and 25 GPs a cholelithogenic high-cholesterol diet (HCD) After 2 weeks, GPs were anaesthetized, GBs opened, bile examined for GS, and a GB catheter attached to a pressure transducer CCK-8 was administered IV in graded doses and intrabiliary pressure changes (pressure × duration) measured. In experiment 2, 37 GPs were maintained on HCD and 20 GPs on ND for 2 weeks. When killed, GBs were opened, bile collected and examined for GS, and GB muscle assayed for CCK receptors (CCK-R) Bile salts, cholesterol and protein concentrations were measured. Statistical analysis was performed by analysis of variance

No GPs on ND developed gallstones. Biliary emptying pressures were significantly reduced in GPs with stones, with an associated decrease in GB CCK-R from $167 \pm 9{\cdot}3$ to $70 \pm 22{\cdot}7$ (no stones to stones, $P < 0{\cdot}05$). There was no difference in bile chemistry between those on a lithogenic diet which did and did not develop stones Diminished GB sensitivity to CCK due to reduced numbers of CCK-R may have an aetiological role in stone formation

Acalculous biliary pain: an alternative explanation

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Abnormal gallbladder function is considered to be the source of symptoms in patients with acalculous biliary pain and cholecystectomy remains the standard treatment. We have used endoscopic retrograde cholangiopancreatography manometry to examine sphincter of Oddi motility before cholecystectomy in 25 patients with acalculous biliary pain. Under diazepam sedation, the papilla of Vater was cannulated with a triple-lumen catheter. This was perfused with degassed water ($0{\cdot}25\,\mathrm{ml}^{-1}\,\mathrm{min}^{-1}\,\mathrm{channel}^{-1}$) using a minimally compliant infusion system Basal and peak pressures were measured and referenced to duodenal pressure. Frequency and direction of propagation of phasic contractions were also recorded. Thirteen patients were given intravenous cholecystokinin (1 unit/kg) and pressure recording repeated 3 min later. At least one of the measured parameters was abnormal in 17 (68 per cent) of the 25 patients Basal pressure was ≥30 mmHg in eight, peak pressure was ≥300 mmHg in five and frequency of contractions was ≥8 min in six. An increase in basal pressure or 'paradoxical' reaction to cholecystokinin was observed in six patients. No patient had >50 per cent retrograde contractions. We have demonstrated sphincter of Oddi abnormalities before cholecystectomy in patients with acalculous biliary pain. These abnormalities may be responsible for the patient's pain and may predispose to the reported high incidence of post-cholecystectomy symptoms in such patients

Plasminogen activators in the re-epithelializing edges of cutaneous ulcers

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Epidermal cellular division and migration are not diminished in the skin surrounding venous ulcers[1], which suggests that poor adhesion or increased cellular loss accounts for delay in healing Local production of urokinase plasminogen activator (u-PA) or tissue plasminogen activator (t-PA) may influence cellular adherence through the ability of plasmin to act on the intracellular linkages of epithelial cells to the basement membrane

Plasminogen activators were measured in skin biopsies from 20 ulcers (9 venous, 11 non-venous). Biopsies from the edge of the ulcer, the adjacent skin, and the ulcer base were homogenized and the supernatants were assayed using a bioimmunoassay for u-PA and t-PA.

t-PA was found in small quantities from the edge of only three ulcers. The levels of u-PA from skin adjacent to the ulcers (median 15·55 units/g tissue) were significantly lower than the levels from the ulcer edges (median 26·13 units/g, Wilcoxon paired rank sum test, $P < 0{\cdot}01$). There was no significant difference in the u-PA levels in the edge compared with the base (median 32·42 units/g, $P > 0{\cdot}10$) of these ulcers. There was no significant difference in the u-PA levels in the skin or ulcer edge of venous compared with non-venous ulcers

The high levels of u-PA found in the edges of all ulcers may represent an epiphenomenon or may be important in influencing ulcer healing Manipulation of local u-PA levels may affect cellular adherence and improve ulcer healing.

1. Adair HM. Epidermal repair in chronic venous ulcers. *Br J Surg* 1977, 64: 800–4.

Effect of the venous abnormality on the course of venous ulceration

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Ascending and descending phlebograms have been performed on 81 limbs after healing of a venous ulcer. The radiological findings were compared with foot volumetry and transcutaneous oxygen measurements.

Forty-one limbs had post-thrombotic changes (18 involving only the calf, 23 extending above the calf), 10 had incompetent communicating veins only, 10 had long saphenous incompetence only, four had femoral vein reflux only, and 16 had no apparent abnormality

There was no significant difference in the transcutaneous oxygen ratio (reading at the liposclerotic area over the reading at the upper arm), relative expelled volume or half volume refilling time on foot volumetry for each of the different appearances on phlebography.

Limbs with post-thrombotic changes extending above the calf had a significantly longer history of ulceration (median >10 years, χ^2 $P < 0{\cdot}01$), longer periods with an unhealed ulcer (median >1 year, χ^2 $P < 0{\cdot}01$) and more recurrences (mean $4{\cdot}2 \pm 2{\cdot}4$, $P < 0{\cdot}05$, Wilcoxon's rank sum test) than limbs with other phlebographic appearances

Phlebography clearly identified one group of limbs that had a poorer clinical course. However, the functional abnormality and the level of skin hypoxia were not significantly worse compared with the limbs with other phlebographic findings. Other factors may be contributing to the poorer clinical course in these limbs.

Laser Doppler waveform analysis and comparison with photoplethysmography in normal and ulcerated lower limbs

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Several studies have examined the absolute values of laser Doppler velocimetry (LDV)-recorded skin blood flow in leg ulcers but scant attention has been paid to the nature of the LDV waveform This waveform has been postulated to represent vasomotor activity and is usually minimized by the use of a heated probe holder producing maximal vasodilation We have noted marked changes in the unheated skin LDV waveform associated with movement of the leg from the elevated to the dependent position

We have examined the nature of the LDV waveform, using an unheated probe holder, in 12 patients (6 with leg ulcers, 6 controls). Measurements were taken 15 cm above the medial malleolus. The variance of LDV waveforms in dependent and supine positioned lower limbs, expressed as a ratio (dependent/supine), was significantly lower in ulcer-bearing ($0{\cdot}36 \pm 0{\cdot}09$, mean ± s.e.m) than in non-ulcerated legs ($0{\cdot}67 \pm 0{\cdot}14$, $P < 0{\cdot}05$). This was also reflected by a corresponding difference in simultaneously recorded photoplethysmographic (PPG) measurement of venous reflux ulcerated limbs ($8{\cdot}7 \pm 1{\cdot}8$ s), non-ulcerated limbs ($29{\cdot}8 \pm 5{\cdot}5$; $P < 0{\cdot}05$)

There was a statistically significant correlation between LDV variance ratios and PPG-measured venous reflux (Spearman's correlation test, $P < 0{\cdot}01$).

We suggest that the comparison of unheated LDV probe waveform changes in the elevated and dependent lower limb offers an alternative method of diagnosing abnormal venous reflux

Role of venous elasticity in the development of venous disease

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A reduction in the elasticity of the venous system has been proposed[1] as a precursor of venous insufficiency, but the concept remains controversial This study was designed to determine venous elasticity in patients with clinically obvious venous disease and in patients with symptoms but no evidence of venous disease

Simultaneous measurements of calf volume (strain gauge) and venous pressure (dorsal foot vein) were made during venous occlusion plethysmography. The elastic modulus, K, defined as stress/strain (P/V) when the veins are full was calculated from the pressure/volume relationship.

In 9 normal legs (N), 25 legs with superficial venous insufficiency (SVI), and 7 legs with deep venous insufficiency (DVI) (classified by Duplex scanning and ambulatory venous pressure measurements) the K value was determined In addition, there were seven legs of a high risk group (HRG) defined by family history of varicose veins and/or standing occupation, with symptoms of ache and swelling but without reflux in superficial or deep veins.

Group	No. of patients	No. of legs	Elastic modulus· K ($\times 10^4$ N m^{-2}) Median	Range
N	6	9	23·92	9·56–60 03
SVI	19	25	1 45	0·40–3·03
DVI	6	7	0 95	0·66–1·16
HRG	6	7	1·08	0·67–2·24

The results (see *Table*) show that the K value clearly separates normal from symptomatic patients, irrespective of venous reflux, suggesting that the onset of symptoms is associated with mechanical changes in the wall and surrounding tissues rather than impaired valve function.

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Protein C activity and postoperative vein thrombosis

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Protein C (PC) is a potent inhibitor of coagulation. Surgery may cause a fall in PC levels[1]. We examined the relationship between PC and the development of venous thrombosis in patients undergoing neorusurgery PC activity, antithrombin (AT III) activity and euglobin clot lysis time (ELT) were measured before surgery (−1), at surgery and on postoperative days 1, 3, 5 and 7. Daily ^{125}I-fibrinogen leg scans were used to detect thrombosis. Patients were grouped as no thrombosis (GI, $n=22$) and thrombosis (GII, $n=9$) There were 12 smokers in GI in contrast to none in GII, and 33 per cent of GI were female in contrast to 66 per cent in GII. Changes in PC were similar in both sexes and in smokers and non-smokers. Pre-operative assays were comparable in both groups. In GI, PC transiently decreased within the normal range, 109 ± 10·0 per cent at (−1) to 94·5 ± 30·3 per cent at (1) ($P<0\cdot03$) and increased towards baseline thereafter. In GII, PC decreased from 104·1 ± 14·3 per cent to 89·6 ± 15 7 per cent at (1), and before returning to baseline, decreased further to 74·8 ± 22 1 per cent ($P<0\cdot01$) at day 3 with two patients showing more than a 50 per cent reduction in PC No significant changes were noted in At III or ELT in either group. The data show that surgery produces a transient reduction in PC activity, which may be prolonged in patients who develop postoperative venous thrombosis. PC may be involved in the pathogenesis of postoperative venous thrombosis.

1. Mannuccio PM, Vigano S. Deficiencies of Protein C, an inhibitor of blood coagulation. *Lancet* 1982; **ii**: 463–7

Venous surgery and ulcer healing: a randomized clinical trial

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Venous ulcers were generally attributed to deep vein disease not easily corrected by surgery, but in over 250 ulcerated legs, superficial incompetence was found in 97 per cent and deep disease in only 42 per cent[1]. Superficial venous surgery has been evaluated in those patients whose venous function was improved by tourniquets

All new patients with chronic venous ulcers (>3 months) were investigated by directional Doppler and ambulatory venous pressures Pressure relief index (PRI) was calculated as the fall in foot vein pressure (mmHg) after 10 tiptoe exercises multiplied by the recovery time (s) Where PRI doubled on tourniquet occlusion of incompetent superficial veins, the patients were randomized to early surgery, but all continued out-patient compression bandaging.

Group	Age (years)	Ulcer size (cm^2)	Ulcer duration (months)	PRI (before surgery)
Surgery ($n=11$)	67 ± 6·5	4·7 ± 1·6	18·2 ± 4	278 ± 15
Conservative ($n=12$)	65 ± 4·7	2·9 ± 0·8	22 8 ± 5	251 ± 18

The results are means ± s e m.

The 23 consecutive patients recruited to date were well matched for age, sex, duration and size of ulcer. PRI was also similar initially, but improved postoperatively to 728 ± 21 in those randomized to surgery ($P<0\cdot001$, Mann–Whitney U). All patients allocated surgery healed by 9 weeks with a mean time to complete healing of 24 ± 3·4 days compared with 75 ± 8 5 days for bandaging alone ($P<0\cdot01$).

Pressure recovery index selects those patients in whom superficial venous surgery will rapidly heal chronic venous ulcers.

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Predicting the chemosensitivity of tumour cells by drug-induced inhibition of their protein synthesis in vitro and of their pulmonary localization after intravenous injection

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Mouse mammary carcinoma cells were exposed *in vitro* to increasing concentrations of Adriamycin (ADR) or 5-fluorouracil (5-FU) Uptake of ^{75}selenomethionine (SeM) in a methionine-deficient medium measured the resulting inhibition of protein synthesis by the tumour cells. This was compared with the ability of the ^{75}SeM-labelled tumour cells to localize in mouse lungs and to form pulmonary tumours after IV injection into isogenic hosts. These parameters were also related to the ability of the drugs to inhibit pulmonary tumour formation *in vivo* when injected into mice which had received tumour cells IV Results from five different tumours were pooled for analysis At the highest drug concentration (10 μg/ml ADR, 100 μg/ml 5-FU), inhibition of protein synthesis was significantly related to the *in vivo* action of the drugs in limiting formation of pulmonary tumours ($P<0\cdot05$ using rank difference coefficient). There was also a direct relationship between pulmonary localization of tumour cells, after exposure to drugs, their ability to form tumour nodules ($P<0\cdot005$) and the *in vivo* action of the drugs in inhibiting tumour formation ($P<0\cdot05$). Thus, inhibition of protein synthesis *in vitro* and pulmonary localization after IV injection may be of value in predicting the *in vivo* effect of cytotoxic drugs.

Detection of malignancy by nuclear magnetic resonance (n.m.r.) spectroscopy of plasma

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The early detection of cancer by a simple haematological test has been the goal of many workers. In 1986 Fossel[1] reported that the mean line widths of the methyl and methylene resonances (Fossel line width) in the water-suppressed n.m.r. spectrum of plasma were correlated with the presence or absence of malignancy. We have analysed plasma from four groups of patients to assess this method further.

Plasma was obtained from 31 patients with untreated breast or gastrointestinal cancer, 24 patients admitted for elective surgery and 22 healthy volunteers

The mean Fossel line width was not significantly different in the four groups (*Table*). However, the methylene peak width was slightly lower in cancer patients than in the control groups ($P<0·05$). A small molecule was detected in the plasma of 10 of 11 breast cancer patients but was found in none of the healthy volunteers ($P<0·001$)

We have been unable to reproduce Fossel's results but more subtle changes in the plasma n.m.r spectrum may ultimately prove useful. The detection of a small molecule in the plasma of breast cancer patients merits further investigation.

Table *Characteristics of the plasma n.m r. spectrum in four groups of patients*

	Patients (*n*)	Fossel line width (mean ± s.e.m.)	Methylene peak width (mean ± s.e.m)	Small molecule detected (*n*)
Breast cancer	11	22·60 ± 0·79	20·82 ± 1·13	10
GI cancer	20	24·34 ± 0·87	22·86 ± 1 1	10
Elective surgery	24	24·82 ± 0·70	23·31- '·06	10
Healthy volunteers	22	24 12 ± 0·61	23 39 ± 0·93	0

1. Fossel ET, Carr JM, McDonagh J. Detection of malignant tumours: Water-suppressed proton nuclear magnetic resonance spectroscopy of plasma. *New Engl J Med* 1986, **315**: 1369–76.

Application of chromosome-mediated gene transfer to the study of metastasis

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Chromosome-mediated gene transfer results in the transfer of subchromosomal fragments of DNA between cells. This technique has been used as a tool for isolating and cloning selected fragments of the mammalian genome[1].

We have used this technique in an attempt to transfer the metastatic phenotype from a highly metastatic murine cell line (CMT 167/10 C6) to a non-metastatic human cell line (EJ) and thereby to isolate metastasis-related genes. Chromosomes from the mouse cells were co-transferred with a selectable marker into the human cells. Selection was applied for human cells which had taken up exogenous DNA. Five independent cell lines were obtained The metastatic ability of these five cell lines was then assessed after subcutaneous injection into nude mice. Three out of five mice injected with one of the cell lines (EJEcol/167CHR E) developed lung metastases. There was no evidence of metastasis in any of the mice injected with cells from the other four cell lines Reinjection of cells established from one of these metastases (AE 2447 2L) produced further metastasis to the mouse lung. The presence of the selectable marker and the mouse DNA sequences in the metastatic human cells was confirmed by Southern transfer and filter hybridization. These results indicate that the selection of metastatic variants from non-metastatic cells after chromosome transfer may prove to be a useful approach for isolating and cloning metastasis-related genes.

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NK cell killing of rat myeloma and carcinoma cells is inhibited in the presence of plasma

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Natural killer (NK) cells play a part in the immune response to tumours[1]. Suppression of this response may explain the adverse effect of blood transfusions during cancer surgery[2]. The aim of this study was to determine whether plasma constituents influence NK cell activity against (1) conventional NK target cells or (2) mammary carcinoma cells.

NK cell assays were performed using a rat splenocyte preparation as effectors and YAC 1 (myeloma) or Mtln3 (rat mammary carcinoma) cells as targets in a 4 h ^{51}Cr release cytotoxicity assay. Control assays were compared with assays in the presence of either 10 per cent citrated rat plasma or 10 per cent rat serum Experiments were repeated after macrophage depletion of effectors.

Rat plasma markedly inhibited NK cell activity (*Table*). This effect persisted whether plasma was syngeneic or allogeneic for the effector cells. Conversely, 10 per cent rat serum had no inhibitory activity. The effect of plasma was not significantly altered by macrophage depletion, indicating that the reduced cytotoxicity was secondary to suppression of NK cell activity.

Table *Mean percentage cytotoxicity at 100·1 effector/target ratio* (*s d.*)

	10% plasma	Control	10% serum
Mtln3	3·6 (3·7)**	12·0 (6·4)**	9·6 (0·5)
YAC 1	12·4 (4·1)*	35·2 (9·5)*	31·7 (11·5)

* $P<0·00001$: ** $P<0·001$; *t* test

Citrated rat plasma markedly inhibits rat NK cell activity against malignant cells. This may represent a regulatory mechanism for NK function, and may have relevance to the adverse effects of blood or plasma transfusion during cancer surgery.

1. Hanna N. Metastatic potential of tumour cells in young nude mice is correlated with low levels of Natural Killer Cell mediated immunity. *Int J Cancer* 1980; **26**· 675–80.
2. George CD, Morello PJ. Immunologic effects of blood transfusion on renal transplantation, tumour operations and bacterial infections. *Am J Surg* 1986; **152**. 329–37

Prediction of progression of prostatic cancer using serum prostate-specific antigen

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The management of prostatic cancer remains a subject of debate. Local disease will progress in only a minority of patients. Once advanced, although hormonal therapy will provide effective palliation, survival will usually not be improved by treatment. An effective method of identifying those tumours which are progressing and require treatment would be of great value to clinicians.

Prostate-specific antigen (PSA) is a recently described serum marker specific to the prostate. It has been shown to be more sensitive than, and distinct from acid phosphatase. One hundred and thirty men have been followed up for 4–26 months (mean 10 months). Fifty-seven with localized disease had an initial mean serum level of 66 ng/ml. Disease progression occurred in 13 men (22·8 per cent), in every case serum PSA rose in parallel. In all cases with stable local disease serum PSA remained static. Eighty men with prostatic cancer and bony metastases had an initial mean PSA of 622 ng/ml (11–4000 ng/ml). Disease progression was judged by isotope bone scan and standard British Prostate Group criteria. Of 28 men with progression of their metastatic disease, 27 had a rising serum PSA and in 92 per cent levels began to rise more than 2 months before clinical relapse. It is concluded that serial PSA estimations are valuable for identifying progressive prostatic cancer in order that early therapy may be instituted.

Correspondence

Perforated duodenal ulcers

Sir

I concur with your leading article concerning perforated duodenal ulcer (*Br J Surg* 1987; 74: 81–2). The implication that unnecessary definitive surgery in the acute state of management should be avoided must be correct, but why not take the argument one step further?

The overall mortality rate today for patients with perforated peptic ulcer treated surgically is approximately[1–4] 5 per cent. This is of the same order as that reported for conservative management in 1956[5]

A recent prospective randomized trial of non-operative *versus* operative treatment for perforated duodenal ulcer[6] has demonstrated the possibility of treating certain groups of patients by non-operative means.

Such a treatment regimen would allow the subsequent definitive surgery to be undertaken on a properly selected group of patients at time of relapse during medical therapy. Using this regimen as many as 75 per cent[6] of all patients suffering perforation of a duodenal ulcer may completely escape the need for surgical intervention

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1. Greco PS, Cahow CE. Alternatives in the management of acute perforated duodenal ulcer. *Am J Surg* 1974; **127**. 109–14.
2. Boey J, Wong J, Ong BG. A prospective study of operative risk factors in perforated duodenal ulcers. *Ann Surg* 1982; **195**: 265–9.
3. Sawyers JL, Herrington JL Jr, Mulherin JL Jr, Whitehead WA, Mody R. Acute perforated duodenal ulcer *Arch Surg* 1975, **110**: 527–30.
4. Coutsoptides T, Himal HS. Perforated gastroduodenal ulcers. *Am J Surg* 1976; **132**: 575–30.
5. Seeley SF, Campbell D Nonoperative treatment of perforated peptic ulcer; a further report. *Int Abstr Surg* 1956; **102**: 435–36
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Growth rate of tumours

Sir

We refer to the paper by Fiennes (*Br J Surg* 1988; **75**: 23–4) which compares the volume estimated by weighing tumour casts with that obtained by caliper techniques.

Whilst approving of the proposed method which is independent of shape assumptions, we dispute in principle the extent of the improvement claimed and note two numerical errors.

The second formula for volume in *Table 3* is the well known formula for the volume of an ellipsoid (volume $= (\pi/6) \times$ length $\times$ width $\times$ depth) with the unmeasured depth equated to the width. The first formula can be obtained from the second by approximating π by 3. Although this is a standard formula, it is clearly inappropriate for estimating the volume of the semi-ovoid cast prepared by the author and would not be used in practice. A semi-ovoid object is closer to a semi-ellipsoid than to a whole ellipsoid The first formula applied to a semi-ovoid should therefore be.

$$\text{Volume} = \text{length} \times \text{width}^2/4$$

which gives a volume of 400 μl for the cast instead of 800 μl. This is only 112 per cent of the true volume compared with the 225 per cent shown in *Table 3*. Similarly, the estimate from the second formula is 418 μl instead of 837 μl giving 118 per cent of the true volume rather than the value shown in *Table 3* which should actually be 235 per cent instead of 250 per cent or 230 per cent as in the abstract.

The third formula refers to diameter, D, which has no standard definition for 3-dimensional objects. Assuming that it is the mean of the length and width here, formula 3 is similar to half the second formula in which diameter is effectively defined as the weighted geometric mean of length and width $\sqrt[3]{(L \times W^2)}$ This is therefore an appropriate formula for the volume of a semi-ovoid giving an over-estimate as stated although it is actually 62 per cent rather than 65 per cent.

Hence, if the semi-ovoid cast is acknowledged as such, the first and econd formulae are not too inaccurate with over-estimates of only 2 per cent and 18 per cent respectively. *Table 4* shows that the volume of the tumour cast under-estimates tumour weight by 12 per cent partly because tissue density may be > 1 and partly because any invasion of the implant is not included. Thus if the caliper technique is used in this case, the errors from different sources are of a similar order and may well compensate for each other.

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Author's reply

I am grateful to Messrs Pritchett and Coleman for pointing out a significant typographical error which escaped proof-reading. It is of course quite true that 837 ÷ 356 gives 235 per cent and this is the figure that should appear in *Table 3*. I used the figure of 230 in the abstract to indicate the general order of magnitude.

It is always possible to devise an approximation formula which gives a good estimate of tumour volume for any given shape As the authors point out, this would need to be a different formula depending on the shape of the tumour. I thought I had made it clear in the discussion (second paragraph, second sentence) that the accuracy of my method could be expected to be largely independent of tumour shape. It is a fact of experience, when dealing with tumour xenografts in nude mice, that the shape of tumours may differ widely between individuals. I suspect that the formulae I quoted from the world literature gained currency among workers with considerable experience in the field, precisely because of this variability I do not think it would be satisfactory, when considering individual animals among a set of replicates, to arbitrarily change from one formula to another in pursuit of tumour shape.

Lastly, my 'semi-ovoid cast' was the cast of a real bilobed subcutaneous nodule, entirely atypical of subcutaneous tumour xenografts in nude mice, as studied by the authorities whose formulae I have quoted.

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For debate: Meleney's synergistic gangrene

Sir

I am the W. H. Cole who, with M. L. Heideman, published an article in the 1929 *JAMA* describing a gangrenous ulceration of the skin developing after drainage following appendectomy (*Br J Surg* 1988, **75**: 267–71). The lesion resembled the progressive gangrenous ulceration of Meleney, but we could not demonstrate the bacterial synergism in spite of the fact that we had available a very competent microbiologist. Consequently we diagnosed the lesion as amoebic, especially since the area had been connected with the intestinal tract (through the appendix)

Dr Frank Meleney was a close friend of mine. He came by St Louis one day to see me. I showed him the slide in which I had identified some amoebae (as trophozoites), but he felt sure they were not trophozoites. This really did roughen our friendship considerably for years.

Another thing which I could not identify as logical was the fact that surgical excision of the gangrenous area was always followed by success by all clinics, and not followed by a flare up of the pyogenic organisms supposedly present

Almost all the surgeons reporting on these lesions have called attention to the remarkable similarity between the two lesions. It would appear that they should be caused by the same aetiological factor, but there are so many inconsistent features in both lesions that such a proposal does not appear totally valid.

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Bleeding gastric ulcers

Sir

We read with interest the assertion by Rogers *et al.* (*Br J Surg* 1988, 75 16–17) that undersewing alone is an effective treatment for bleeding gastric ulcers Their conclusion is based upon an historical review of patients in which no comparison has been made between the types of ulcers that were being treated or the incidence of multi-organ failure

In our experience, the undersewing of shallow gastric ulcers, where the bleeding is mainly from a mucosal source, produces satisfactory results. However, undersewing of chronic and deep gastric ulcers may be technically difficult and is associated with a higher rate of rebleeding. Unfortunately, the authors do not comment on the type of ulcers that were selected for each form of therapy. In addition, some bleeding gastric ulcers are malignant. This factor has not been commented on by the authors.

When comparing the mortality rate from the various operations used to treat bleeding gastric ulcers, the authors commented that '. . no explanation for these differences in mortality could be found'. This is hardly surprising as the incidence of organ failure is perhaps the most important index of survival after this type of surgery In a well constructed clinical trial it would be important to demonstrate that there was a baseline equivalence for this variable between the groups under study. Several objective indices of the severity of acute illness have been published, e.g. the APACHE score. Other factors such as age, sex, severity of bleed, delay before surgery, and grade of surgeon should be interpreted with regard to the physiological reserves of the patients.

We would, therefore, take issue with their conclusion All that one might deduce from the paper of Rogers *et al* is that selected patients can be safely treated by the mere undersewing of their bleeding gastric ulcers The reasons that led to these patients being selected for that form of therapy are unclear. This paper therefore adds nothing to our knowledge of the surgical management of patients with bleeding gastric ulcers and we agree with their safe comment that 'Simple undersewing plus biopsy should be considered as an effective surgical treatment for patients requiring intervention for haemorrhage from a gastric ulcer'.

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Authors' reply

Sir

The letter from Chleboun and Hall raises three main points about our study: the incidence of multiple organ failure, the size of gastric ulcers treated and the problem of malignant gastric ulceration. We quite agree that the presence of concomitant disease leading to postoperative organ failure following surgery for bleeding gastric ulceration is an important factor in determining outcome. Indeed, our policy of minimizing surgical trauma recognizes this concept. We believe that risk factors for organ failure were evenly distributed among our study groups but accept that in a prospective study quantitative assessment would be valuable. All patients reported in our study underwent surgery for continuing bleeding or rebleeding from a gastric ulcer with endoscopically verified major stigmata of haemorrhage and thus no 'shallow gastric ulcers' with bleeding 'mainly from a mucosal source' were included in our study. Finally, in our experience, malignant gastric ulceration can invariably be recognized at endoscopy or during surgery and to date no unsuspected malignancies have been revealed by biopsy during haemostatic surgery Furthermore, routine postoperative endoscopy at 1–2 months in these patients serves as a check both on healing and the absence of malignancy.

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'Button-hole' incisional hernia

Sir

The recent interest in 'button-hole' incisional hernia (*Br J Surg* 1987, 74· 824–5 and *Br J Surg* 1988; 75 187) draws attention to the fact that most techniques for repair of midline abdominal incisions result in stress directed parallel (or at least oblique) to the direction of fibres of the rectus sheath. Hence it is not surprising that some sutures may have a 'sawing' effect, either early or late This can also occur with the 'far near–near far' suture widely recommended for difficult cases because of its mechanical advantage over simple suture. However, the pulley effect transfers the main tension to the 'far' elements of the stitch—located within the rectus muscles/rectus sheath.

To overcome this disadvantage we introduced a double near and far stitch 15 years ago (*Figure*), particularly for repair of incisional hernia, but for all wounds where extra strain on the abdominal wound may be anticipated in the postoperative period This suture carries the mechanical advantage of the simple near and far stitch but the tension is maintained by the link element at either end—directed at right angles to the fibres of the rectus sheath. Although it is likely that someone has used this suture technique in the past, we have not been able to find a report of it.

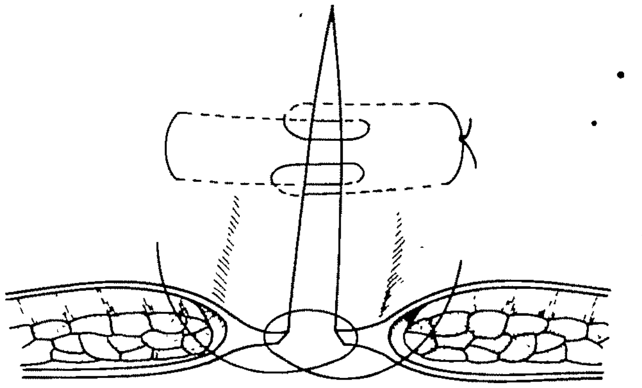

Figure *The elements of the single near and far suture, and the 'double near and far' formed from two single sutures in parallel*

No case of 'button-hole' incisional hernia has been seen in many hundreds of difficult wounds and incisional hernias repaired in this way. Furthermore, repair with this stitch is satisfactory using No. 3·5 metric polypropylene or nylon suture, thus minimizing the volume-related adverse effects often attributed to the suture material rather than to the use of unnecessarily thick sutures.

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Colorectal carcinoma

Sir

We read with interest the article by Finan (*Br J Surg* 1987; 74· 945–7) and the subsequent correspondence by Greig and Miller (*Br J Surg* 1988, 75 293). We agree entirely with Mr Finan's comment that all patients undergoing surgery for colorectal carcinoma should be screened for synchronous tumours. However we disagree with the suggestion by Greig and Miller that the missed synchronous tumour may not influence long term survival and, for purposes of prognosis, can be classified as recurrent disease This conclusion cannot be drawn from the work of Tornqvist[1] who did not specifically look at recurrent disease due to missed synchronous tumours. In any case for recurrence to occur one usually assumes that a tumour has been initially removed

For a number of years it has been our policy to perform a double contrast barium enema or colonoscopy on all patients with colorectal carcinoma. While we recognize that colonoscopy is the ideal method of pre-operative assessment it is often not practicable in many centres to colonoscope all patients before surgery. We usually reserve colonoscopy for cases where a good double contrast barium enema has been equivocal or has demonstrated polyps.

Between January 1987 and February 1988 we have treated 87 patients with colorectal carcinoma. Eight patients had synchronous tumours (9·2 per cent) There was a total of 11 synchronous tumours only 2 of which had a better Dukes' classification that the index tumour Only one patient was not diagnosed pre-operatively. In this case a synchronous carcinoma was found at laparatomy while performing a palliative defunctioning colostomy.

Our experience suggests that the incidence of synchronous colorectal carcinoma is higher than commonly reported Although the number of patients is small they do represent a consecutive series which has been fully investigated prospectively This is in contrast to many reports which are retrospective and include substantial numbers of inadequately investigated patients.

If, as we believe, nearly 10 per cent of colorectal carcinomas may be multiple then is it negligent not to fully investigate all patients presenting with a colorectal carcinoma?

1. Tornqvist A, Ekelund G, Leander L. Value of intensive follow-up after curative resection for colorectal carcinoma. *Br J Surg* 1982, 69: 725–8.

A. Wyman
K. Rogers

Excision of anal transition zone

Sir

We would like to raise certain points regarding the Keighley *et al.* study (*Br J Surg* 1987; **74**: 1118–21).

Firstly, we believe that the sensory information provided by the anal transition zone is of importance in the continence and discrimination only when the anorectal inhibitory reflex is present, otherwise the anorectal 'sampling' should not take place. The conclusion of the authors that excision of the anal transition zone does not increase the risk of impaired continence after restorative proctocolectomy is in accordance with the finding that absence of anorectal inhibitory reflex after ileo-anal anastomosis does not affect continence[1].

Secondly, the authors also point out that despite objective loss of anal sensation after excision of the anal transition zone most patients retain the ability to discriminate gas for semisolid stool. We wonder when those patients retain the ability to discriminate gas straining at stool and/or before defaecation takes place? In absence of the anal transition zone and anorectal inhibitory reflex, discriminations would only be possible during defaecation, when neorectal contents contact with the lower anal canal (the anal transition zone and anorectal inhibitory reflex avoid false call to stool in healthy man?).

So to preserve the anal transition zone has only logic when leaving a long rectal muscular sleeve to provide anorectal inhibitory reflex. If we consider that the sensory arm of the ileo-anal continence is of importance, then the anal transition zone should be preserved and long mucosectomy performed.

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J. Camuñas

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1. Taylor BM, Beart RW, Dozois RR, Kelly KA, Wolff BG, Ilstrup DM. The endorectal ileal pouch–anal anastomosis: current clinical results. *Dis Colon Rectum* 1984; **27**: 347–50.

Authors' reply

Sir

The recto-anal inhibitory reflex was absent in all of the patients reported in our study, irrespective of the length of preserved anal mucosa. However, in all these patients the entire rectum was excised. We believe therefore that a rectal muscle sleeve may be necessary to retain the recto-anal inhibitory reflex. Despite loss of the recto-anal inhibitory reflex and anal sensation in the majority of patients in our series, discrimination was preserved—they could pass wind during normal activities, not just during defaecation and did not leak faeces. These clinical observations cast doubt on the importance of the recto-anal inhibitory reflex and anal transition zone as the modulator of discriminatory anorectal function.

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Recurrent ulceration after parietal cell vagotomy

Sir

We read with interest the recent paper by Hoffman *et al.* (*Br J Surg* 1987; **74**: 1056–9). They reported 30 per cent proven recurrent ulceration 14–18 years after parietal cell vagotomy. We would like to present our results following parietal cell vagotomy. The short term recurrent ulcer rates in our series have been previously published[1,2]. Questionnaires were sent to 242 patients who had undergone elective parietal cell vagotomy for duodenal, pyloric and prepyloric ulcers and who had completed 5–15 years follow-up. Symptomatic patients were offered a gastroscopy. The general practitioners of deceased patients were sent a short questionnaire requesting information as to the cause of death and the presence or absence of any peptic symptoms. Of the 242 patients, 183 were available for assessment; 59 patients were lost to follow-up. In all, 33 patients reported symptoms of whom 29 attended for endoscopic assessment.

A total of 155 patients were graded as Visick I or II; 7 patients had recurrent symptoms without ulcers and were graded Visick III; 21 patients were graded Visick IV (13 with a chronic duodenal ulcer, 7 with a transient ulcer and 1 with outlet obstruction).

Out of 183 patients, 20 (11 per cent) had developed a recurrent ulcer in our study group. Of the 20 recurrences, 14 occurred up to 5 years after surgery. A further 5 recurred within 6–10 years after surgery and only 1 recurrence occurred 11 years after surgery. On Hoffmann's criteria, 7 of our recurrences could be classified as transient/innocuous (35 per cent) and the remaining 13 as chronic/malevolent (65 per cent). This would give our series a chronic recurrent ulcer rate of some 7·1 per cent.

In Hoffmann's series, 13 of 32 recurrences (41 per cent) occurred 10–17 years after surgery. Their results cast a shadow on the long term efficacy of parietal cell vagotomy for duodenal ulceration. In contrast our recurrent ulcer rate over 5–15 years in 183 patients was only 11 per cent, with most occurring in the first 5 years after surgery. This compares favourably with figures in the literature which range from 11 to 25 per cent[3] over similar follow-up periods. In our opinion, these results would justify the continued use of parietal cell vagotomy in the surgical treatment of duodenal ulceration.

A. Masters
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F. I. Tovey
R. J. Heald
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1. Makey DA, Tovey FI, Heald RJ. Results of proximal gastric vagotomy over 1–5 years in a District General Hospital. *Br J Surg* 1979; **66**: 39–42.
2. Tovey FI, Heald RJ, Teague D, Durkin F. Correspondence. *Br J Surg* 1981; **68**: 293.
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Oesophageal carcinoma: combined chemo- and radiotherapy

Sir

We endorse Professor Hennessy's views regarding the use of combined pre-operative chemo- and radiotherapy in patients with oesophageal carcinoma (*Br J Surg* 1987; **75**: 193–4). Initial results from this hospital using a regimen of 5-FU, cisplatin and 30 Gy of radiotherapy have shown encouraging responses[1].

Our further experience has been equally encouraging with 15 of 19 and 5 of 11 patients with squamous cell and adenocarcinoma of the oesophagus, respectively, demonstrating complete post-therapy, endoscopic tumour resolution: 11 of 19 and 6 of 11 of the above patients have shown no histological oesophageal or nodal tumour in the resected specimens.

The combined chemo- and radiotherapy regimen has also proven of great benefit as palliative therapy: 31 of 42 patients were rendered free of malignant dysphagia until the time of death from distant disease. This regimen has reduced, substantially, our reliance on palliative intubation for irresectable disease.

Contrary to Professor Hennessy's opinion, however, pre-operative chemo- and radiotherapy has in our experience not increased the early mortality. Perioperative deaths occurred in 5 of 30 patients, 2 due to respiratory failure and 3 to cardiovascular causes.

The role of pre-operative chemo- and radiotherapy is, as yet, undefined in the strategy of therapy for oesophageal carcinoma. We are encouraged by these early results and, particularly so, for those patients with oesophageal adenocarcinoma. Despite some reports of impressive surgical results, the overall perioperative mortality following oesophagectomy remains high[2]. We question whether trials of pre-operative chemo- and radiotherapy, using traditional surgery as the control arm, are necessary. We are embarking on a trial in which we administer combined chemo- and radiotherapy to all patients with oesophageal carcinoma and randomize those who demonstrate endoscopic and histological resolution into two groups: one group to undergo oesophagectomy and the other to receive continued surveillance, and to undergo surgery if and when local tumour occurs.

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G. G. Jamieson
P. G. Gill

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1. Denham JW, Gill PG, Jamieson GG *et al.* Preliminary experience with a combined-modality approach to the management of oesophageal cancer. *Med J Aust* 1988; **143**: 9–13.
2. Earlam R, Cunha-Melo JR. Oesophageal squamous cell carcinoma. 1. A critical review of surgery. *Br J Surg* 1980; **67**: 381–90.

Book reviews

Auf dem Weg zur Physiologischen Chirurgie. Der Nobelpreisträger Theodor Kocher 1841–1917

U. Tröhler. Pp 240+xvi. Illustrated. 1984. Basel, Boston, Stuttgart: Birkhäuser Verlag. £19.10.

Theodor Kocher of Berne was one of the greatest figures in the surgical revolution of the late 19th and early 20th centuries. A new biography by the Professor of medical history at Göttingen gives a scholarly and fascinating account of his life and work and of his close relationships with his contemporaries. Who was Kocher and what sort of man was he? What did he achieve and how did he do it? Why was he great?

Theodor Kocher was born in Berne in 1841 and spent most of his life there. Before qualifying in 1865, he visited Theodor Billroth who was then in Zürich, and there he met Spencer Wells—both men were to influence him greatly. He worked briefly for Professor Bernhard von Langenbeck in Rudolf Virchow's laboratory in Berlin. In 1866 he was appointed assistant to Professor Georg Lücke in Berne, and undertook experiments into blood clotting and haemostasis, combining basic and applied research. He succeeded Lücke in 1872, at the age of 31, and occupied this chair until his death in 1917.

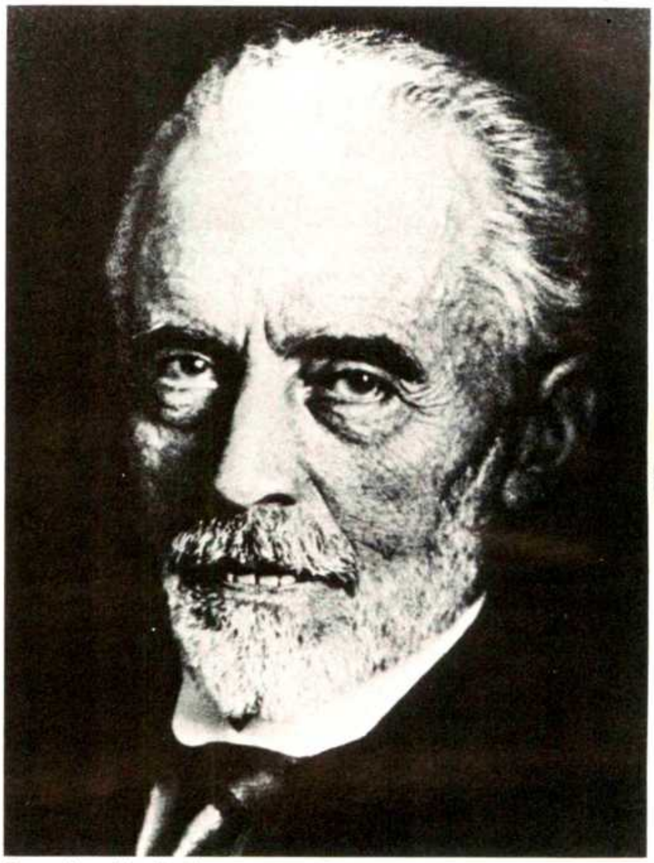
Kocher was a single-minded, dedicated man of religious temperament; he was reserved, disciplined, systematic and meticulous in all that he did. Harvey Cushing, who worked with him, described him as a perfect surgical technician. He was happily married for over 50 years and had three sons, two of whom assisted him. Despite his reserve, he welcomed visitors into his home.

Experimental physiology and pathology, for which Kocher was indebted to John Hunter and his school, formed the basis of his clinical surgery, and his laboratory research included studies of wound healing, surgical bacteriology, antisepsis and intracranial pressure. He was a very general surgeon, whose original work included operations on the abdominal and pelvic viscera, the central nervous system, hare lip and cleft palate, club foot, hernia, the pituitary, the ovaries, the breast, and varicose veins. His name is applied to many operations and procedures, including reduction of the dislocated shoulder and mobilization of the head of the pancreas (which he popularized, but did not originate); his chart for mapping the level of spinal chord injuries was in use for many years. He learned from Spencer Wells the value of analysing and publishing audits of his work, and he did so regularly for thyroidectomy and many other operations. One result was his conclusion that radical operations were often valuable, if undertaken early, especially for gastric cancer and for tuberculosis of bones and joints.

Kocher's greatest contributions were in thyroid surgery, and he published his results as each 1000 operations were completed (7052 eventually). The mortality rate fell from 40 per cent (the general rate at that time) to 0·2 per cent for simple goitre. This was accomplished by early adoption of antisepsis and asepsis, strict haemostasis, and steady improvements in operative technique. As was usual then, Kocher removed thyroid lobes completely because partial resection was more haemorrhagic. This resulted in total thyroidectomy when both lobes had to be removed to relieve tracheal obstruction. In 1882 he found that 16 of 18 patients thus treated were severely handicapped mentally and physically, developing a condition which he named 'cachexia strumipriva'. Later this was identified with cretinism in children and myxoedema in adults, all of which were found to be due to thyroid deficiency. As a result of his experience, Kocher abandoned total thyroidectomy for benign disease, experimented with thyroid transplantation, successfully treated his cachectic patients with thyroid extract, and finally with 'thyro-albumen', produced in his own laboratory. Over-dosage resulted in thyrotoxicosis, providing support for the view that this was due to hyperthyroidism.

These achievements were the direct result of Kocher's personal qualities: his creativity and his ready acceptance of new concepts such as antisepsis, his recognition of flaws in his practice as revealed by regular audit, and his readiness to change. He stimulated all who worked with him and collaborated actively with others: Lord Lister in antisepsis, Victor Horsley in thyroid surgery, Horsley and William MacEwen in cranial surgery, Spencer Wells in haemostasis and statistical analysis, George Crile in surgical shock, William Halsted in local anaesthesia and hernia, Cushing in hypophysectomy, and many others. He travelled widely and received many visitors and research assistants, particularly from Europe and America. He wrote classic textbooks, including his famous *Operative Surgery* which was translated into several languages, including English, and wrote over 200 papers.

His greatness was the result of these qualities and achievements which were recognized worldwide. He was invited to accept other prestigious chairs but preferred to stay in Berne which he had made a surgical Mecca. His many professional and civil honours included Honorary Fellowship of The Royal College of Surgeons of England in 1900 and, crowning all, the Nobel Prize '...for his works on the physiology, pathology and surgery of the thyroid gland.' in 1909.



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Professor Tröhler helps us to appreciate this surgical pioneer who built bridges between the 19th and 20th centuries and across the world, and whose basic ideas and principles are still valid. His life and work repay careful study and an English edition of this book would be welcome.

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Cancer of the Face and Mouth. Pathology and Management for Surgeons

I. A. McGregor and F. M. McGregor. 225 × 282 mm. Pp. 606. Illustrated. 1986. Edinburgh: Longman. £100.00.

The surgical management of head and neck cancer is currently undertaken by a number of different specialities. Whether the surgeon is ENT, general, oral or plastic, success depends on a thorough knowledge of surgical anatomy, surgical pathology and, more than in most fields, techniques of repair. The authorship of this book represents a particularly happy combination of a pathologist and a plastic surgeon whose experience of the disease process and its surgical ablation is matched by his skill in reconstruction—an area where he has made such a great contribution.

The scope of the book is the face, oral cavity and major salivary glands. After a general chapter on reconstructive methods, each specific site is considered in systematic fashion, starting with anatomy and proceeding to pathology, clinical aspects, technique of resection and choice of repair. This entails some degree of repetition but means that each chapter can be read as a self-contained entity. This is very much a personal testimony as is reflected in liberal reference to individual patients, telling illustrations and a characteristically practical, no-nonsense approach. The bibliography is likewise selected and strictly to the point. The reader is left with a clear idea of the operative management of any tumour likely to be encountered in the face and oral cavity. Herein, however, a note of caution is required because the authority of presentation and clarity of description of how to do it is not quite matched by an emphasis on when to do it. Radiotherapy is allotted only 5 pages in a 600 page text and, while the essence of its role in general has been beautifully crystallized, the unfamiliar reader will gain no concept of its value in managing cancers of the face and lips. Likewise, the importance of irradiation in reducing the incidence of neck failure after cervical node dissection receives no mention.

The authors have largely omitted statistical data on the grounds that they create a false aura of accuracy. While this argument has some validity, there is a danger that personal impression may be equally misleading One might question the inability to take seriously the suggestion that osteosarcoma of the facial bones has a better than average prognosis. Perineurial spread of squamous carcinoma does imply an adverse prognosis, notwithstanding the authors' feelings to the contrary

These criticisms however in no way detract from the stated purpose of the volume which is to guide the surgeon who operates in this testing area. Within these terms of reference it is a major achievement and is likely to remain unsurpassed for a long time to come.

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Orthopaedics. The Principles and Practice of Musculoskeletal Surgery

S. P. F. Hughes, M. K. D'A Benson and C. L Colton. 250 × 185 mm. Pp. 1077. Illustrated. 1987. Edinburgh Churchill Livingstone. £125.00.

This book sets out to approach the study of orthopaedics in a novel manner by linking the basic sciences with the diagnosis and treatment of the different diseases. It varies from the standard orthopaedic textbook in its departure from the usual region by region approach. Whilst this is largely successful, there are one or two sections where various unrelated topics are thrown together, for example biomechanics, radiology and genetics. According to the Editors, this book is aimed at orthopaedic surgeons in training, particularly those preparing for the specialist examinations in orthopaedics. As with all multi-author books, there are inevitably difficulties in achieving a common standard, for instance some of the early chapters appeared to be pitched more at an undergraduate level whereas others were clearly aimed at the postgraduate student. The other problem, common to all multi-author textbooks, is the period of gestation from writing to publication. This has meant that some of the sections, particularly in the field of joint replacement, have been overtaken by events; for instance, resurfacing techniques in the hip have been largely abandoned and there is now more interest in uncemented types of arthroplasty. I particularly liked the chapters on muscles and nerves, genetics, the hand, and rehabilitation. The general layout of the book is excellent but many of the radiographs have not reproduced well on the printed page. Despite these criticisms this book has been well edited and is easy to read with a good index and reference list. I would certainly recommend it as a reference textbook for the orthopaedic library; however, I think the individual orthopaedic trainee might be better served by studying review articles and monographs on individual subjects.

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Clinical Hemorheology

S. Chien, J. Dormandy, E. Ernst and A. Matrai. 245 × 160 mm. Pp. 387+xi. Illustrated. 1987. The Hague. Martinus Nijhoff Publishers. £65.75.

Haemorheology, the study of blood flow, is a relatively new multidisciplinary science which this compact book comprehensively covers from both the scientific and the clinical aspects The first part is devoted to the principles of haemorheology and the second to the clinical relevance of the many rheological abnormalities found in certain disease states.

The physical laws relating to blood flow are first outlined, followed by an account of the use of viscometry, aggregometry, and blood filtration to determine the effects of blood cell concentration, plasma viscosity, and cell aggregability and deformability on blood flow A detailed account then follows of how red and white blood cells may affect blood flow, and of the relevance of the geometry of the vascular tree. The first part is completed by a discussion of the relevance of rheological factors in terms of physiology and pathophysiology.

The remainder of the book relates to clinical practice, with an examination of the rheological abnormalities and their management in a number of clinical disorders. These include cardiovascular disease, arterial and venous thrombosis, haematological disorders, diabetes, and several others such as low flow states. The significance of haemorheology in obstetrics, neonatology and gynaecology is also discussed. The chapter on treatment describes the use of haemodilution, apheresis, plasma substitutes, defibrinogenation, and a variety of drugs

The message of this book is that while rheological abnormalities are common, and may be important in many disease states, there is still a great need for well designed, controlled studies to determine what is cause and what is effect and whether rheological manipulation is of value in terms of prevention and treatment. There will doubtless be further editions and, if so, it would be helpful to have a list of contributors at the front and to make the last chapter, which is an overview, the introduction. Also, the index could be expanded to include topics such as smoking and dehydration. *Clinical Hemorheology* is a text for the institutional library, and for those with a particular interest in the subject

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Northfield's Surgery of the Central Nervous System. Second edition

J. D. Miller. 194 × 252 mm. Pp 891. Illustrated 1987. Oxford Blackwell Scientific. £120.00.

In my first weeks of training in neurosurgery, I read two books cover to cover, Brain's *Neurology* and *Northfield's Neurosurgery*. The latter book was perfectly pitched midway between the cheap, single volume introductions to neurosurgery, designed for senior house officers and fellowship candidates, and the expensive multivolume, multi-author American books designed for libraries. Northfield, in a single well written volume, covers a whole range of the speciality and is full of excellent, clinical descriptions, sound advice and superb references. Its only failing is that, for my generation, it is out of date Mr Northfield's death occurred before he could revise the text to include many of the advances that we now take for granted, most notably CT scanning.

This new edition, edited by Douglas Miller, is an excellent volume which has been thoroughly updated without losing the additional elements of the original. Rather than a single author, ten authors are now used and it has become effectively the Merseyside textbook of neurosurgery Seven of the authors are from that unit and they contribute 17 of the 24 chapters. The chapters are laid out as in the original and have been truly revised and updated rather than rewritten, allowing much of Northfield's clinical descriptions to be retained. The revising has been cleverly done and the book is only 40 pages longer than the original. Illustrations and references are many and first class

The book is well produced, with good quality binding and paper and, as a result, expensive but I feel anyone who seriously considers a career in neurosurgery, world-wide, should consider it a good investment. All trainees should read it from cover to cover and return to it regularly and every department should have a copy in its library. Our registrar has already obtained his own copy and those who wish to succeed should do likewise.

P. Richards

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Notices and announcements

20–22 June 1988

7th International Workshop for the Study of Vascular Anomalies

Hamburg, Germany

Information: Professor Dr D. A. Loose MD, Jurgensallee 44, Hamburg 52, FRG

24–25 June 1988

British Association of Surgical Oncology Summer Meeting

Stockton-on-Tees, UK

Information British Association of Surgical Oncology, Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

27–28 June 1988

Serotonin Explored: what it does and how it can be manipulated for therapeutic purposes

London, UK

Information· Miss Penny Robinson, IBC Technical Services Ltd, Bath House, 56 Holborn Viaduct, London EC1A 2EX, UK

29 June–1 July 1988

International Symposium on Therapeutic Progress in Urological Cancers

Paris, France

Information Dr Saad Khoury, Clinique Urologique (Pr Chatelain), Hôpital de la Pitié-83, Boulevard de l'Hôpital, 75634 Paris Cedex 13, France

3–9 July 1988

16th World Congress of the International College of Surgeons

Milan, Italy

Information Secretariat, Clinica Chirurgica III—Universitá degli Studi, Via F Sforza 35, 20122 Milan, Italy

6–8 July 1988

Tripartite Meeting: Joint Meeting of the Surgical Research Society, the European Society for Surgical Research and the Society of University Surgeons

Bristol, UK

Information: Mr D J. Leaper, Southmead Hospital, Bristol, UK

10–14 July 1988

XII Biennial Congress of the International Society of University Colon and Rectal Surgeons

Glasgow, Scotland, UK

Information· Dr H.S. Crum, Programme Chairman, Wick, Caithness, UK

14–16 July 1988

XIIIth International Update on Liver Disease

Royal Free Hospital, London, UK

Information· Professor N McIntyre, Academic Department of Medicine, Royal Free Hospital, Pond Street, London NW3 2QG, UK

27–31 July 1988

International Symposium of Inflammatory Heart Disease. A Multidisciplinary Approach to Myocarditis and Heart Allograft Rejection

Colerado, USA

Information. Ms Marge Adey, Continuing Education, University of Nebraska Medical Centre, 42nd and Dewey Avenue, Omaha, NE 68105-1065 Nebraska, USA

14–19 August 1988

XII International Congress of the Transplantation Society

Sydney, Australia

Information· Congress Secretariat, 145 Macquarie Street, Sydney, NSW 2000, Australia

28 August–1 September 1988

Fifth World Conference on Lung Cancer

Interlaken, Switzerland

Information· Fifth World Conference on Lung Cancer, c/o AKM Congress Service, PO Box 6, CH-4005 Basle, Switzerland

30 August–2 September 1988

10th World Congress Collegium Internationale Chirurgiae Digestive

Copenhagen, Denmark

Information· Secretariat, Spadille Congress Service, Sommervej 3, DK-3100 Hornbaek, Denmark

4–8 September 1988

11th Annual Meeting of the European Neuroscience Association

Zurich, Switzerland

Information· 11th Annual Meeting of the European Neuroscience Association, c/o AKM Congress Service, PO Box, CH-4005 Basel, Switzerland

8–10 September 1988

Annual Meeting of the Association of Surgeons in Training

Belfast, UK

Information. Mr Bernard Lee, Department of Surgery, Belfast City Hospital Tower, Lisburn Road, Belfast BT9 7AB, UK

10–18 September 1988

Fourth Annual Fall Ultrasound Symposia

London, UK

Information· Annual Fall Ultrasound Meeting, Medical Seminars International Inc., 21915 Rosco Boulevard, Suite 222, Canoga Park, California 91304, USA

12–14 September 1988

International Hepatobiliary Pancreatic Association

Nice, France

Information. Dr Jean Mouiel, Department of Surgery, Hôpital Saint Roch–BP319, 06006 Nice Cedex, France

14–16 September 1988

Royal College of Surgeons of England Annual Meeting of Fellows and Members

Cambridge, UK

Information Secretary, Royal College of Surgeons of England, 35/43 Lincoln's Inn Fields, London WC2A 3PN, UK

18–23 September 1988

The Second Oxbridge Organ Transplantation Course

Cambridge, UK

Information. Director, Courses Department, The British Council, 65 Davies Street, London W1Y 2AA, UK

26–30 September 1988

Royal Microscopical Society Ultrastructural Anatomy Course

Belfast, UK

Information: The Administrator, Royal Microscopal Society, 37/38 St. Clements, Oxford OX4 1AJ, UK

20 October–5 November 1988

Expanding Horizons of Diagnostic Ultrasound

Bath, UK

Information: Director, Courses Department, The British Council, 65 Davies Street, London W1Y 2AA, UK

4–7 November 1988

The XXVIth IUAT World Conference on Tuberculosis and Respiratory Diseases

Singapore

Information, Professional Postgraduate Services, K.K., Singapore Representative Office, 20 Kramat Lane #03-07, United House, Singapore 0922

25–26 November 1988

European Symposium on Ultrasonic Radiation Safety

Copenhagen, Denmark

Information: Mrs A. G. Thorn, Ultrasound Laboratory, Glostrup Hospital, DK 2600 Glostrup, Denmark

25–27 November 1988

22nd Annual Combined Surgical Meeting

Singapore

Information· The Secretariat, 22nd Annual Combined Surgical Meeting, Academy of Medicine, Singapore College of Medicine Building, 16 College Road, Singapore 0316

13–18 December 1988

Annual Convention of The American Academy of Neurological and Orthopaedic Surgeons

Las Vegas, USA

Information Dr M R Rask, Programme Chairman, 2320 Rancho Drive, Suite 108, Las Vegas, Nevada 89102-4592, USA

27–30 December 1988

Association of Surgeons of India Golden Jubilee Annual Conference

New Delhi, India

Information Dr N C. Madan, Organizing Secretary 'ASICON-88', Room No. 5034, Department of Surgery, All India Institute of Medical Sciences, New Delhi - 110029, India

19–23 February 1989

7th Congress of the Association of Surgeons of South East Asia

Penang, Malaysia

Information Congress Secretariat, 7th Congress Asian Surgical Association, c/o Tawakal Specialist Centre, 198A-208A Jalan Pahang, 53000 Kuala Lumpur, Malaysia

MAY 1988

The American Journal of Surgery®

VOLUME 155

NUMBER 5

CONTENTS

PAPERS OF THE NORTH PACIFIC SURGICAL ASSOCIATION

PRESIDENTIAL ADDRESS

632 Recollections, Responsibilities, and Rewards of a Senior Surgeon
R. EDWARD ROBINS

SCIENTIFIC PAPERS

635 Human Amnion as a Bioprosthesis for Bile Duct Reconstruction in the Pig
CHARLES H. SCUDAMORE, CHRISTOPH D. BECKER, J. STEPHEN FACHE, RODOLFO BIANCO, CHRISTOPHER R. SHACKLETON, H. JOACHIM BURHENNE, DAVID A. OWEN, MARTIN T. SCHECHTER, and DAVID SECCOMBE

641 Pancreatitis Associated With Pancreas Divisum: Results of Surgical Intervention
CONRAD H. RUSNAK, ROBERT T. HOSIE, PETER M. KUECHLER, JAMES D. McHATTIE, JAMES R. PIERCEY, and ROBERT D. CAMERON

644 Long-Term Patency of Polytetrafluoroethylene Graft Fistulas
EARL S. SCHUMAN, GEORGE F. GROSS, JOHN F. HAYES, and BLAYNE A. STANDAGE

647 Antegrade Aortorenal Bypass Graft: A New Alternative
HUGH G. BEEBE and STEVEN D. MacFARLANE

651 Magnetic Resonance Imaging Versus Angiography in the Preoperative Assessment of Abdominal Aortic Aneurysms
STANLEY J. RUFF and MILTON R. WATSON

655 Treatment of Infected Abdominal Aneurysms by Extraanatomic Bypass, Aneurysm Excision, and Drainage
LLOYD M. TAYLOR, Jr., DAVID M. DEITZ, DONALD B. McCONNELL, and JOHN M. PORTER

659 Hepatocellular Carcinoma. A Comparison of Oriental and Caucasian Patients
CHARLES H. SCUDAMORE, JOSEPH RAGAZ, ANDREAS M. KLUFTINGER, and DAVID A. OWEN

663 Hepatocellular Carcinoma: Importance of Histologic Classification as a Prognostic Factor
WILLIAM J. WOOD, MAURICE RAWLINGS, HAROLD EVANS, and CHRISTOPHER N. H. LIM

667 Pharmacokinetics, Toxicity, and Short-Term Results of Cisplatin Hyperthermic Isolated Limb Perfusion for Soft-Tissue Sarcoma and Melanoma of the Extremities
RODNEY F. POMMIER, H. STEPHENS MOSELEY, JORDAN COHEN, CHU S. HUANG, RAEANN TOWNSEND, and WILLIAM S. FLETCHER

672 Cytotoxicity of Dimethyl Sulfoxide and Antineoplastic Combinations Against Human Tumors
RODNEY F. POMMIER, EUGENE A. WOLTERING, GEORGE MILO, and WILLIAM S. FLETCHER

677 Percutaneous Endoscopic Gastrostomy
WILLIAM SANGSTER, GARY D. CUDDINGTON, and BEN L. BACHULIS

680 Acute Graft-Versus-Host Disease of the Intestine. A Surgical Perspective.
GREGOR I. McGREGOR, JOHN D. SHEPHERD, and GORDON L. PHILLIPS

683 Management of Carcinoma Discovered Unexpectedly at Operation for Acute Appendicitis
JAMES J. PECK

686 Repeat Parathyroid Operation Associated With Renal Disease
PHILIP T. ALEXANDER, EARL S. SCHUMAN, R. MARK VETTO, GEORGE F. GROSS, JOHN F. HAYES, and BLAYNE A. STANDAGE

690 Individualized Management of Colonic Atresia
ELIZABETH C. POHLSON, EDWIN I. HATCH, Jr., PHILIP L. GLICK, and DAVID TAPPER

693 Introducer Insertion of Mini-Thoracostomy Tubes
STEVEN W. GUYTON, DANIEL L. PAULL, and RICHARD P. ANDERSON

697 Aortic Dissection. A Six Year Experience With 117 Patients
GUY FRADET, W. R. ERIC JAMIESON, MICHAEL T. JANUSZ, A. IAN MUNRO, HILTON LING, ROBERT T. MIYAGISHIMA, and G. FRANK O. TYERS

701 Lower Extremity Revascularization With In Situ Saphenous Vein for Critical Ischemia
MILTON H. BRINTON, CHRISTOPHER STAHLER, and GERALD GIBBONS

704 Impact of Advanced Trauma Life Support Training on Early Trauma Management
JUDITH A. VESTRUP, ANNE STORMORKEN, and VICTOR WOOD

708 Patterns of Injury in Helmeted and Nonhelmeted Motorcyclists
BEN L. BACHULIS, WILLIAM SANGSTER, GUY W. GORRELL, and WILLIAM B. LONG

712 Right Ventricular Dysfunction in Multiple Trauma Victims
A. CRAIG EDDY, CHARLES L. RICE, and DOREEN M. ANARDI

716 Letters to the Editor

717 Book Reviews

718 ***The British Journal of Surgery*** **Table of Contents (vol. 75, no. 4, Apr. 1988)**

A20 Information for Authors

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References

1. Wittmann, D.H., *et al.*, Proc. 21st ICAAC, 1981: 404. 2. Fredlund, H., *et al.*, Proc. 12th ICC 1981, **1,** 700. 3. Morris, D.L., *et al.*, *J. Hosp. Inf.* 1983, **4:** 159-164. 4. Leigh, D.A., *J. Antimicrob. Chemother.* 1984, **13,** 525-567. 5. Nicoletti, P., *Drugs Exper. Clin. Res.*, 1983, **9** (8-9): 609-624. 6. Hoogkamp-Korstanje, J.A.A., *et al.*, *J. Antimicrob. Chemother.* 1981, **8,** 101-106. 7. Viollier, A.F., 2nd Int. Symp. Infec. Immunocomp. Host 1983, 172-174. 8. Sanders, C.C., *J. Antimicrob. Chemother.*, 1984, **13,** 1-3. 9. Taylor, E.W., *et al.*, *J. Int. Med.*, 1983; **11:** 28-31. 10. Wittmann, D.H., and Schassan, H.H., Proc. Piperacillin Symp. (Munich) 1980, 142-152. 11. Pipril Product Information Book. 12. Minami, S., *et al.*, *Antimicrob. Ag. Chemother.*, 1980, **18,** (3), 382-385.

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